DOCUMENTATION

for

BONE HEALTH DATA

in

MIDUS 2
BIOMARKER PROJECT
(P4)

University of Wisconsin ♦ Institute on Aging
March 2018

INTRODUCTION

This document provides an overview of the bone health data collected in the MIDUS 2 Biomarker Project (P4) data. The scope of data collected was expanded over the course of the data collection period. This document describes the evolution of the bone health measures and also provides comprehensive information regarding methods used to collect data about bone health. Administrative and computed variables are also identified and information about the construction and usage of these variables is included.

Data users are also encouraged to review the Biomarker (P4) Readme Data File Notes. This document provides information about naming conventions, as well as administrative and filter variables included in the data file. It also includes information about how we handled missing values and other issues that arose over the course of the study. For example, there are instances when variables were added or sections of an instrument were expanded for data entry purposes to accommodate additional information provided by the respondent.

This document will be periodically revised and updated as more information is gathered, and researchers continue to work with the MIDUS 2 Biomarker data. If there are suggestions or comments, please contact midus_help@aging.wisc.edu.

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SECTION A

OVERVIEW OF DATA FILE AND COLLECTION PROTOCOLS

OVERVIEW OF DATA FILE AND COLLECTION PROTOCOLS

The Biomarker Project (P4) includes multiple types of data regarding bone health, from the indicated sources, as follows:

- Bone Turnover measures from serum.
- Dual Energy X-ray Absorptiometry (DXA) Scans (EXPANDED)
    - Bone Density
    - Bone Strength Indices
    - Body Composition
- Questionnaire Data

As described in the "MIDUS 2 Biomarker Project (P4) Readme Data File Notes", naming convention organizes variables according to data type or the method used for data collection. We have followed this convention with respect to the bone health data, thus analysts using bone turnover, densitometry, and questionnaire data will need to pull variables from different sections of the data file. Details about these data appear below.

Due to funding limitations, the bone densitometry scans and questionnaire were added to the Biomarker protocol months or years after the data collection period began. The following text provides details about the development of the overall bone health protocol, as well as additional details about the measures.

Bone Health Data Collection Timeline

In contrast to other aspects of the Biomarker data collection, the comprehensiveness of bone health measures has changed over time and between sites as follows:

August 2004 – P4 data collection begins, blood samples collected from all study participants for Bone Turnover Assays:

- BSAP (Bone Specific Alkaline Phosphatase)
- NTx (n-teleopeptide type 1 collagen)
- P1NP (aminoterminal propeptide type 1 procollagen)
- Serum Creatinine

October 2004 – Support from the General Clinical Research Center (GCRC) at the University of Wisconsin-Madison (Site 2) allows Bone Densitometry scans and a Bone Questionnaire to be added to the protocol at this site.

Summer 2005 - December 2005 – Supplemental funding was obtained from the National Institute on Aging. The Bone Densitometry Scan Protocol was expanded to all 3 sites. The Bone Questionnaire was also expanded to include questions about smoking and exercise history. The UW site was already conducting bone scans thus the bone questionnaire was implemented in July 2005 at Site 2. The other two sites began conducting bone scans and administering the bone questionnaire in the Spring 2006.

May 2007 – The Bone Densitometry Scan Protocol was expanded to include a Whole Body scan to measure 3 compartment total body composition (bone, fat, and lean) as an additional objective indicator of obesity. To facilitate interpretation of these data items regarding metal in the body were added to the Bone Questionnaire. These changes

were implemented in June 2007 at UW (Site 2), August 2007 at UCLA (Site 1), and February 2008 at Georgetown University (Site 3).

Data Documentation

Bone Turnover:
The bone turnover assays use samples that are processed through the Biocore. Thus, this data can be found with the other blood assay result data. Details about the blood collection and processing protocols can be found in the "Documentation for Blood, Urine and Saliva Data".

Following the MIDUS variable naming convention, the first three characters of these variables are "B4B".

Bone Questionnaire:
The bone questionnaire is a standalone instrument administered by project staff during the clinic visit. A copy of the questionnaire appears in Section 2 below with variable names inserted below or next to the items. The variable names begin with their own unique 3 character set "B4O".

Variables for the bone questionnaire appear in the data file immediately after the items from the Medical History.

Densitometry Scans:
As noted above, the DXA scan protocol was expanded in May 2007 to include a whole body scan. The whole body data was not included in the initial MIDUS 2 Biomarker data release but are now included in the updated aggregate file. The protocols for both the bone densitometry and whole body scans appear in Section 3 below. However there are some site specific idiosyncrasies.

1. The University of Wisconsin (UW, Site 2) is the central coordinating site and is responsible for all QC tasks.

2. UW had been collecting bone densitometry data for the lumbar spine (L1-L4, both hips, and the non-dominant forearm) for several months when funding was received to support collection of DXA data at the other two sites. To accommodate differences among the three sites the protocol described in the manual includes just scans of the *lumbar spine* (L1-L4) and *left femur*. All 3 sites follow the protocol in the manual for these 2 scan sites. To maintain consistency locally, however, the protocol already in use at Site 2 (UW) continues to include the right femur and the non-dominant forearm.

3. Sites 1 (UCLA) and 3 (Georgetown) use Hologic systems, while Site 2 uses a GE Lunar system. Due to significant differences in BMD as measured by Hologic and GE, we created two sets of mutually exclusive variables, one for Hologic data and one for Lunar data. Thus, UW cases only have Lunar data, while UCLA and Georgetown cases only have Hologic data.

ANALYSIS NOTE: The BMD values from the Lunar and Hologic systems are not directly comparable, but there is good agreement between the T-scores generated by these systems. Thus, it is recommended that T-scores be used in analyses involving the full set of bone scan data. For more information see the following citations.

Hanson, J. (1997). “Letter to the Editor Standardization of femur BMD.” Journal of Bone and Mineral Research 8:1316-1317.

Kiebzak, G., E. M. Lewiecki et al. (2004). “Good diagnostic agreement using T-scores between Delphi and Prodigy.” Journal of Clinical Densitometry 7:229.

Kiebzak, G.M, N. Binkley et al (2007). “Diagnostic agreement at the total hip using different DXA systems and the NHANES III data base.” Journal of Clinical Densitometry 10:132-137.

For data analysts interested in using *just* proximal femur data the following citation provides equations for converting Lunar data to Hologic for *women*.

Lu, Y., T. Fuerst, et al (2001). “Standardization of bone mineral density at femoral neck, trochanter and Ward’s triangle.” Osteoporosis International 12:438-444.

For body composition data, conversion equations are available for BMC, BMD and percent fat in the citation below.

Shepherd J, Fan B et al (2012). “A multinational study to develop universal standardization of whole-body bone density and composition using GE Healthcare Lunar and Hologic DXA systems.”

Variables

The bone densitometry variables appear in the data file immediately following the bone questionnaire data. The variable names begin with “B4D” and include the following measures:

1. Bone Density:
    a. Spine - Bone mineral density (BMD) for L1-L4, T-score for L1-L4
    b. Femur (one side only)
        i. BMD for the Trochanter and Neck regions as well as Total Femur
        ii. T-score for Neck and Total Femur

        Note: BMD data from both hips is available for most of the subjects from UW (see # 3 above). In those instances the lowest value was selected for inclusion in this dataset.
    c. Forearm-
        i. BMD for the Ultradistal (UD) and 1/3 radius
        ii. T-score for 1/3 radius

2. Bone Strength Indices – variables indicating femoral neck strength relative to load. The protocol for creating these variables and related background information can be found in Section D below.
    a. Compression Strength Index g/kg-m
    b. Bending Strength Index g/kg-m
    c. Impact Strength Index g/kg-m

3. Body Composition – measures of bone, fat, and lean mass in grams for:
    a. Arms – right, left, both
    b. Legs – right, left, both
    c. Trunk – right, left, both
    d. Total – right, left, both
    e. Android
    f. Gynoid

The data set also includes the following more administrative variables:

- B4DAVAIL – categorical variable indicating whether there is scan data available for a given case.
- B4DNARSN – categorical variable linked to B4DAVAIL indicating the reason for partial or missing bone density data.
    - Scheduling Problem – scan couldn't be scheduled due to the respondent's travel schedule.
    - Technical Problem – scan not done due to technical difficulties/problems at the time of the scan.
    - Scan Not Scoreable – scan was done but couldn't be scored. This occurred most often due to the presence of metal rods in the bone.
    - Visit Terminated- clinic visit was terminated due to acute respondent health problems.
    - R refused – participant decided not to participate in this part of the protocol.
    - INAPP – this variable is not relevant because all bone densitometry data are available (B4DAVAIL =1) or the individual completed the clinic visit before bone densitometry scans were available at the site (B4DAVAIL=9).
- .B4DSTYPE -The scanner system (Lunar, Hologic) used to collect the data.
- Region specific variables indicating the side (left or right) scanned for the individual femur areas and the radius.
    - B4DTRSID - Femur Trochanter side scanned, 1=Right, 2 = Left
    - B4DFNSID - Femur Neck side scanned, 1=Right, 2 = Left
    - B4DFTSID - Femur Total side scanned, 1=Right, 2 = Left
    - B4DRSIDE - Radius side scanned, 1=Right, 2 = Left

SECTION B

BONE QUESTIONNAIRE

Bone Questionnaire

ID #:_____ Site:_____ Date: _____

History of Falls and Broken Bones

1. As an adult, have you ever broken a bone from a simple fall (i.e., a fall from standing height or less that did not involve trauma or loss of consciousness)? [B4O1] **Yes No (Go To 2)**

Bone broken	**Please describe the circumstances**	**Age when this occurred**
a. [B4O1A1W]		[B4O1A3]
b. [B4O1B1W]		[B4O1B3]
c. [B4O1C1W]		[B4O1C3]

2. Has one of your immediate family members (blood relatives) had a broken bone from a simple fall as an adult? [B4O2] **Yes No (Go to 3) Don't Know (Go to 3)**

	Hip Fracture	**Vertebral Fracture (Back bone)**	**Fracture elsewhere**
Mother	Yes No [B4O2A1]	Yes No [B4O2A2]	Yes No [B4O2A3]
Father	Yes No [B4O2B1]	Yes No [B4O2B2]	Yes No [B4O2B3]
Sibling	Yes No [B4O2C1]	Yes No [B4O2C2]	Yes No [B4O2C3]

3. How many times have you fallen in the last year? _[B4O3]____**(If 0 go to Q4)**

3a. How many of those falls were simple falls?____[B4O3A]_____

Medical Conditions ID#_____

4. Have you ever had any of the following conditions?

Parathyroid disease or elevated blood calcium	[B4O4A]	**Yes**	**No**	**Unsure**
Cushing syndrome (or elevated cortisol)	[B4O4B]	**Yes**	**No**	**Unsure**

Medication History

5. Have you ever received any medication(s) for osteoporosis treatment, such as alendronate (Fosamax), risedronate (Actonel), zoledronic acid (Zometa), calcitonin (Miacalcin), raloxifene (Evista), teriparatide (Forteo) ? [B4O5]

Yes (Go To 5a) No (Go To 6)

5a) If YES, what medication(s) and for how long (Ex. Ages 47 – now)?

Medication	Begin Age	End Age	Ongoing
[B4O5A1AM]	[B4O5A1B]	[B4O5A1C]	[B4O5A1CO]
[B4O5A2AM]	[B4O5A2B]	[B4O5A2C]	[B4O5A2CO]
[B4O5A3AM]	[B4O5A3B]	[B4O5A3C]	[B4O5A3CO]

6. Have you ever taken/had any of the following medications/treatments?

		If Yes:	
		Name of medication	**When?** Ex: Age 47-54
a. Medication to treat seizures or epilepsy	**No Yes Unsure** [B4O6A1]		
b. Chemotherapy for cancer	**No Yes Unsure** [B4O6B1]		
c. Immunosuppressive therapy (to treat auto-immune diseases or to prevent transplant rejection)	**No Yes Unsure** [B4O6C1]		
d. Prednisone (cortisone)	**No Yes Unsure** [B4O6D1]		
e. Birth control pills (oral)	**No Yes Unsure** [B4O6E1]		
f. Post-menopausal hormone therapy (estrogen, progesterone) or in men: testosterone therapy	**No Yes Unsure** [B4O6F1]		

Smoking, Passive Smoking, and Exercise History ID#_____

7. Have you now or in the past used tobacco regularly? [B4O7] **Yes No (Go To Q11)**

8. For how many years did you smoke regularly (at least a few cigarettes every day)? [B4O8]

9. During this period, how many cigarettes did you smoke per day, on average? _[B4O9]____

10. For how many years did you regularly smoke a pipe or cigars, or use snuff or chewing tobacco?___[B4O10]

11. In the past (as an adult), did anyone in your household smoke tobacco *inside* your home regularly (at least a few cigarettes, 1 cigar, or 1 pipe bowl every day)? [B4O11] **Yes No**

12. When you were aged 14-18, how many years did you participate in...

    a. Competitive Sports _[B4O12A]_ **years**

    b. Recreational Sports _[B4O12B]_ **years**

    c. Little exercise beyond PE classes _[B4O12C]_ **years**

    (Interviewer: Every year in high school without participation in competitive or recreational sports should be counted in the 3rd category: little exercise beyond PE.

13. After high school, between the ages of 20 and 35, were there periods when you engaged in regular physical activity (for at least 20 minutes at a time, at least 3 times a week), either at work, at home/garden, in sports, or for exercise? [B4O13] **Yes No (Go To 15)**

    We define 3 general types of regular exercise or activity. It can be:

    VIGOROUS- Which causes your heart to beat so rapidly you can feel it in your chest and you perform it long enough to work up a good sweat and breathe heavily (e.g., competitive sports, running, vigorous swimming, high intensity aerobics, digging in the garden, or lifting heavy objects.

    MODERATE-Which causes your heart rate to increase slightly and you typically work up a sweat (e.g., leisurely sports like light tennis, slow or light swimming, low intensity aerobics or golfing without a power cart, brisk walking, mowing the lawn with a walking lawnmower).

    LIGHT - Which requires little physical effort (e.g., light housekeeping like dusting or laundry, bowling, archery, easy walking, golfing with a power cart or fishing)

14. When you were between the ages of 20 and 35 how many years did you participate in regular physical activity (for at least 20 minutes at a time, at least 3 times a week)…

    a. Vigorous level _[B4O14A]__years

    b. Moderate level _[B4O14B]__years

    c. Light level ___[B4O14C]___years

ID#_____

Is R female? [B4O14X] Yes No (Go To 23)

Women's Health (For women only)

15. Have you ever been pregnant? [B4O15] **Yes No (Go To 17)**

16. How many pregnancies did you carry to term? _[B4O16]_____

16a. How many total months did you breast feed? (Add up over all pregnancies): _[B4O16A]___

17. Have you had a menstrual period in the last year? [B4O17] **Yes No (Go To 20)**

18. Have you had a menstrual period in the last 3 months? [B4O18] **Yes No (Go To 20)**

19. Compared to a year ago, has your menstrual cycle length (the number of days between the start of one menstrual period and the start of the next menstrual period) become less predictable / regular (i.e., differences in cycle length more than 7 days)? [B4O19]

Yes (Go to 22) No (Go To 23)

20. When was your last menstrual period?__ **years and____months ago** [B4O20Y]
21. Did your menstrual periods stop because of a reason other than natural menopause? [B4O21] **Yes No Unsure**

    21a. If yes or unsure, indicate ALL SUSPECTED reasons:

    1. Medication, chemotherapy, or radiation ☐ [B4O21A1]
    2. Severe weight loss ☐ [B4O21A2]
    3. Hysterectomy (surgical removal of uterus) ☐ [B4O21A3]
    4. Surgical removal of both ovaries ☐ [B4O21A4]

    [B4O21A5]

22. When did you first notice irregularity in your menstrual cycle length (cycle length variability 7 days or more)? ____ **years and_____months ago** [B4O22Y]

ID#_____

Metal implanted in your body

The following questions are about metal joints or other metal devices that you may have in your body. [B4O23X]

23. Do you have a pacemaker? [B4O23] **Yes** **No**

24. Do you have an implanted pump for medication (e.g. insulin or pain medication pump)? [B4O24]

Yes **No**

25. Do you have any artificial joints? [B4O25] **Yes** **No (Go To 26)**

a. Knee [B4O25A]	**Yes**	**No**
b. Hip [B4O25B]	**Yes**	**No**
c. Other [B4O25C]	**Yes**	**No**

26. Do you have any rods, plates, or screws, or pins in your bones or joints? [B4O26] **Yes** **No (Go To 27)**

Rod or Plate Location		
a. Lower extremity [B4O26A]	**Yes**	**No**
b. Upper extremity [B4O26B]	**Yes**	**No**
c. Spine [B4O26C]	**Yes**	**No**
d. Elsewhere [B4O26D]	**Yes**	**No**
Pin Location		
e. Hands or feet [B4O26E]	**Yes**	**No**
f. Elsewhere [B4O26F]	**Yes**	**No**

27. Do you have any other metal in your body that cannot be removed (includes rings, body piercings, etc)? [B4O27]

Yes **No (End)**

If YES, what is the metal and where is it located?

Specify other metal type	**Where is it located?**

SECTION C

BONE DENSITOMETRY SCAN PROTOCOL

BONE DENSITOMETRY PROCEDURES

MIDUS II BIOMARKER (PROJECT 4)

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CONTACT INFORMATION

DXA/IQC Related Issues:

1. _____

2. _____

3. _____

Study Specific Protocol Issues:

DXA OPERATOR'S SIGN-OFF

This is to insure that all DXA technologist read and fully understand what will be expected from their site for the BMD procedures portion of the MIDUS study. The material in this manual should be read and understood prior to scanning the first subject. All DXA technologists directly involved with the study must sign and date this form to acknowledge and confirm understanding of DXA requirements for the MIDUS biomarkers supplement study.

Please fax a copy of this form to designated staff. The original is to be kept with the study DXA binder at the site.

DXA Technologist (s):

Printed Name and Date (First and Last)	Signature	Initials

INTRODUCTION TO QUALITY ASSURANCE

The purpose of this manual is to standardize DXA scanning procedures among clinical centers participating in the MIDUS study. Bone mineral density is an important endpoint in this study. As such, excellence in obtaining these data are critical. Success will depend on several factors, including qualifications and dedication of the DXA technologists, clear understanding of the study requirements and good communication between the clinical sites, study investigators and UW Osteoporosis Research DXA QA Center.

Site Responsibilities

- Monitor DXA scanner performance throughout the study duration.
  1. Daily QA
  2. Phantom QA
  3. Notify UW DXA center of all hardware problems or replacements
  4. Notify UW DXA center of all software problems or upgrades

- Ensure that BMD measurements are skillfully and consistently acquired for each subject, following the procedures in the Manufacturer's Operator's manual and this manual.
  1. Subject demographic entry
  2. Subject BMD scan modes
  3. Subject BMD positioning and acquisition
  4. Subject BMD data back-up and archived

- Data transmission to the UW Osteoporosis Research DXA QA Center
  1. Subject BMD scans
  2. Instrument Quality Control data

UW Osteoporosis Research DXA QA Center

- Monitor the performance of all densitometers used for acquisition of BMD data in this study and provide a summary of scanner performance at the study conclusion
  1. Collect all QA data from study sites
  2. Analyze, maintain and validate QA data
  3. Assure that sites submit all QA and study participant data in a timely manner

- Assure consistent acquisition and analysis of subject scans among individual densitometry sites
  1. Analyze and retain all images for every subject
  2. Retain BMD data in an orderly fashion for the duration of the study

- Assure that study sites have proper supplies needed for BMD data transmission
  1. Study specific BMD forms

CROSS CALIBRATION

The purpose of cross calibration is to ensure that bone mineral density (BMD) measurements at different clinical study sites may be compared. Your site cannot start scanning subjects until cross calibration has been completed. Your site will be contacted as to when you may start scanning subjects.

You will receive a BoneFide® encapsulated phantom before the study begins. You will be contacted to determine a time that this phantom will arrive at your site; please have the cross calibration done in a timely manner. Each site will scan the phantom ten times on the same day without repositioning. A courier service will be used to deliver and forward the phantom to the next study site after cross-calibration scan completion. You will need to send media with the electronic copies and the cross calibration form to the UW DXA Center when completed.

INSTRUCTIONS FOR CROSS CALIBRATION

Patient Biography

The first patient in the new database for this study will be the cross calibration phantom. Please create the patient biography in a new database if possible for the GE Lunar phantom as follows:

MANDATORY INFORMATION
LAST NAME: Cross-Calibration Phantom
FIRST NAME: MIDUS
MIDDLE INITIAL: Leave blank
ETHNICITY: White
SEX: F
BIRTHDATE: 11/11/1951
PATIENT ID: Leave blank
IDENTIFIER 2: Site location (e.g.: UW, UCLA, Georgetown)
REFERRING PHYSICIAN: Leave blank
MENOPAUSE AGE: Leave blank
WEIGHT: 130 lbs or 60 kg
HEIGHT: 65 inches or 164 cm
PATIENT COMMENT: Cross Calibration / Technologist initials

Scan Acquisition

Please set the parameters to the default mode and use array, if applicable.

Position the phantom on the scanner pad after the machine's scan arm has moved to the approximate start position. Position the phantom so that the laser light is on the start position indicated on the phantom. **DO NOT move the laser light, move the phantom to the laser light.** Make sure that the phantom is parallel to the scanner's long axis with the starting mark pointing toward the foot end of the table. The phantom should be approximately in the center of the scanner table.

Begin scanning the phantom. The phantom image should appear in the first 6-10 lines or 1 swipe of the scan. If no phantom image appears in the first 10 lines or the 2 swipes, stop the scan. Reposition the phantom and restart the scan.

Please allow the scan to finish on its own, do not stop it prematurely.

Scan the phantom nine more times. The starting point for subsequent scans will be correct as long as the operator does not move the scanner arm or the phantom between scans.

Scan Analysis

Please use "Auto Analysis" to analyze the spine phantoms. **DO NOT alter bone edges or baselines.** Analyze the L1-L4 region. Do not accept the default analysis. Use the scan image and the histogram to place the intervertebral marker defining L1-L4. Use the compare function to analyze the remaining nine scans, using the first scan as the reference.

DXA SCANNER PERFORMANCE

DAILY QA

Quality assurance should be done at least three times per week and on all days that patients are scheduled to insure stable scanner performance. QA must be done before study patients are scanned.

If the QA does not pass on the first try, please repeat. Make sure that the QA block is positioned correctly. If QA fails twice, please refer to your manufacturer's manual for instructions. DO NOT scan study participants; if QA fails reschedule or cancel the appointment.

PHANTOM QA

Phantom QA should be done at least three times per week using your site's phantom, and on all days that study patients are scheduled. When analyzing phantom scans please use the copy/compare function.

If a phantom baseline is not established at your site, please scan your phantom a total of 25 times in two or more days (e.g. 13/12 scans on two days, 8/8/7 scans on three days or five scans on five days) to establish a baseline. Please follow the instructions below to calculate the mean and 1.5% acceptable range.

Calculating the Phantom Baseline BMD

- Record the results of the 25 phantom scans onto the QA phantom form.
- Add the total of *L1-L4 BMD* values from the 25 baseline phantom scans to determine the sum.
- Divide the sum by 25 to determine the BMD mean.
- Record the mean. The BMD mean will not change unless you recalculate the baseline for your densitometer.
- Determine the acceptable range. This range should be ± 1.5% of the BMD mean.
- Mean = the sum of 25 phantom scans divided by 25.
  +1.5% = mean + (.015 x mean)
  -1.5% = mean - (.015 x mean)

The phantom BMD value should not differ from your mean by > 1.5%. If two consecutive values exceed this, it is recommended that you contact the manufacturer's service department.

HARDWARE PROBLEMS OR REPLACEMENTS

Please notify the UW DXA center by fax if there are any scanner hardware problems during the study and include a copy of the service reports. The UW DXA center must be notified when hardware changes are required. If possible, please scan your QA phantom 10 times before hardware changes are made and 10 times after replacement or service has been done. This is to determine if changes in machine calibration occur.

SOFTWARE PROBLEMS OR UPGRADES

Please notify the UW DXA center if there are any scanner software problems during the study. Ideally, no software upgrades should occur during the study. However, if software changes are scheduled to occur, please notify the UW QA center prior to making this change. Additionally, please scan the QA phantom 10 times before and after such changes are made. This is to determine changes in machine calibration.

ACQUIRING SUBJECT BONE MINERAL DENSITY SCANS

SUBJECTS

All premenopausal women will have a urine pregnancy test performed on the GCRC prior to DXA scan performance

Eligible respondents will be given a Whole Body Scan in addition to the standard spine and femur scans. The screening questionnaire will be administered by project staff before the participant arrives for the bone scan. The technician should review the screening questions with the respondents to confirm eligibility prior to beginning the scan.

SUBJECT DEMOGRAPHIC ENTRY

Subject ID numbers will be assigned by your local site study coordinator. Please fill in the subjects demographic as follows:

Last Name: Patient Initials
First Name: Leave blank
Middle Initial: Leave Blank
Ethnicity: Fill in
Sex: Fill in
DOB: Fill in
Patient ID: (Subject ID – obtain from study coordinator)
Identifier 2: (Site location - e.g.: UW, UCLA, Georgetown)
Referring Physician: (Investigator's Name)
Menopause Age: Leave blank
Weight (kg): Fill in
Height (cm): Fill in
Patient Comment: (MIDUS Study)
(Technologist Initials)

SUBJECT BMD SCAN MODES

Subjects should be scanned in the same modes as routinely done at your site, unless the densitometer defaults or suggest that the scan be done in a specific mode.

SUBJECT POSITIONING AND SCAN ACQUISITION

General Guideline for Subject Scanning

- Describe the scanning procedures to the volunteer.
- Assure that recent GI contrast or nuclear medicine scans have not been done.
- Check to make sure that volunteer does not have any metal around the scanning area (e.g., zippers, belts, coins/keys in pockets, etc.).
- The volunteer should be positioned using the manufacturers positioning devices.
- Ask the volunteer to remain still for the scan duration.

SPINE SCAN PROCEDURES

For spine scans, please include at least half of L5 and T12 and assure that the lowest ribs are visible. All volunteers should be positioned as straight as possible, with a sponge positioner under subject's legs in a 90 degree angle and their hands to the side. The starting location should be approximately two fingers below patients navel, place the laser there. Reposition the volunteer and restart the scanner as necessary.

FEMUR SCAN PROCEDURES

For femur scans, the LEFT femur will be measured. Volunteer's shoes should be removed, the femoral shaft straight, hip optimally rotated using the positioner routinely used at the facility, such that only a small amount of the lesser trochanter is visualized. Palpate the greater trochanter, and align the laser with the knee and the pubis area (laser should be positioned on the individuals thigh at about 1.5 inches below the pubis). The scan should start about five cm below the lesser trochanter and the ischium should be seen within 20 scan lines or two swipes.

WHOLE BODY SCAN PROCEDURES

On Hologic machines, choose the Whole Body of HP Whole Body mode (for obese participants) in the Scan Type list.

Positioning:

Lie the participant oh his/her back with the head at the right end of the table, looking up at the ceiling, arms at the sides with palms down, separated from the thighs, and feet pointing up. Move the table and C arm to the center. Check that

- the body is straight, using the center lines at the head and foot of the table as gauge
- the body (including feet) are within the scan limit border line
- arms are within the scan limit border

Rotate the participants' legs inward 25 degrees till toes touch, then BIND the feet USING A SOFT COTTON STRAP (EG, GAUZE BANCAGE) to maintain position.

Instruct the patient to lay still and breathe normally.

Scan Procedure:
Make sure that the entire body and both arms are in the scan field. If the person is taller than 6 feet, 6 inches, exclude the feet. If the person is wider than the scan width, exclude THE LEFT ARM COMPLETELY AND CAPTURE THE RIGHT ARM. BE SURE THERE IS AIR BETWEEN THE PPTS TRUNK AND THEIR ARMS. Make sure that the participant remains still until the last pass of the C arm.

DATA BACK UP AND ARCHIVING

If possible, please create a separate database for this study. Please backup and archive all study DXA scans daily.

ANALYSIS OF BMD SCANS

Please DO NOT send analyzed patient scans. All patient scans should be sent to the UW DXA center unanalyzed.

SUBJECT BMD SCANS

Subject BMD scans should be sent by FTP Secure FX

- Please ensure that all patient information is accurate
- Subject scans labeled by Hologic software with date and time sent, with an extension containing subject ID;
  - i.e. 0606061122-1456 (datetime-subID)
- Complete and properly filled out BMD Logsheet,
  - label 'Subj' your site scan date, i.e. 'Subj UC 042606.doc'
  - emailed to designated staff
  - Not to be included on FTP site

INSTRUMENT **QUALITY CONTROL (IQC) DATA**

IQC data should be sent monthly in a timely manner.

The following should be enclosed in each shipment:

- A complete QA spine phantom form
- DXA service record form (if applicable)
- DXA technologist information sheet if new technologist acquiring scans

SECTION D

BONE STRENGTH INDICES

Introduction

The following describes the MIDUS 2 bone strength indices data that were constructed from the bone health and physical examination data collected in the MIDUS 2 Biomarker Project (P4).

Composite indices of the strength of the femoral neck relative to load were created by combining bone mineral density (BMD) and size (length and width) of the femoral neck with body weight and height, using previously published formulas derived from structural engineering principles [Karlamangla, et al. 2004].

Hip fractures in older adults represent a major source of morbidity and physical disability [Burge et al. 2007], and the major predictor of hip fracture risk is low bone strength in the femoral neck, a narrow region of mostly cortical bone that connects the femoral head, which is part of the hip joint, with the shaft of the femur (the long bone in the thigh) [Cummings et al 1995; Johnell et al 2005] – See Figure 1 (p. 3 below). The density of bone mineral in the neck of the femur, though important, is not the only driver of its strength – the ability to resist fracture. The size of the femoral neck size also contributes to its structural strength [Alonso et al. 2000; Cheng et al. 1997; Cordey et al 1992], just as the strength of engineering structures depends on both material density and structure size.

To keep fracture risk low, the strength of the femoral neck needs to be high relative to the forces that it is exposed to. Body weight and body height determine the forces that load the bone in a fall [Robinovitch et al. 1991]. The composite indices of femoral neck strength relative to load, therefore combine femoral neck BMD, femoral neck length and width, and body height and weight, to index the ability of the femoral neck to resist fracture in three different failure modes: compression, bending, and impact. These indices have been shown to correctly stratify women by fracture risk, and to predict incident fractures without requiring knowledge of the woman's race/ethnicity – a requirement for risk stratification by BMD [Ayoub et al. 2014; Ishii et al. 2012; Karlamangla et al. 2004; Srikanthan et al. 2014; Yu et al. 2010]

Measures: Composite Strength Indices

Femoral neck BMD and the following two measures of the size of the femoral neck were obtained from dual x-ray absorptiometry (DXA) scans of the hip using automated Hologic software provided by the manufacturer.

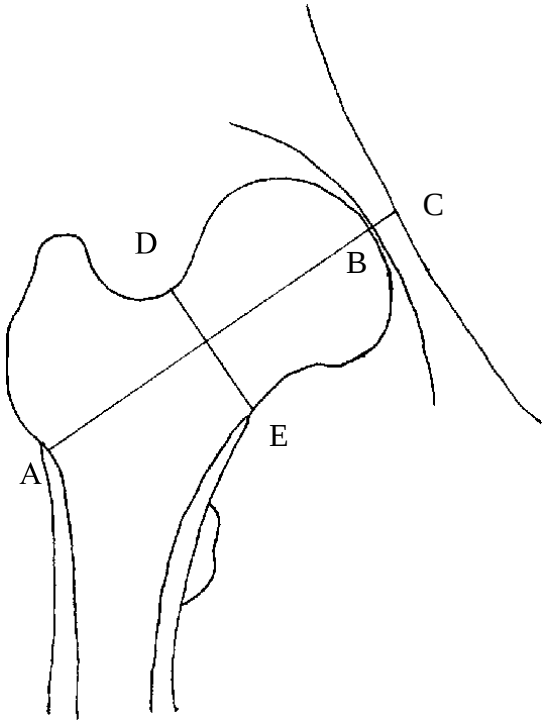
1. Femoral neck axis length (FNAL): the distance along the long axis of the femoral neck from the lateral margin of the base of the greater trochanter to the apex of the femoral head (line A-B in Figure 1).
2. Femoral neck width (FNW): the smallest thickness of the femoral neck along any line perpendicular to the femoral neck axis (line D-E in Figure 1)

As noted in the M2_P4 Bone Data Documentation, two of the three MIDUS clinical sites, UCLA and Georgetown, used Hologic DXA scanners, and the third site, University of Wisconsin, used Lunar DXA scanners. All scans were analyzed centrally at the University of Wisconsin.

Lunar scanners measure both the left and right femur, while Hologic scanners measure one side. Per convention, data reported are for the left femur in every participant, unless the participant had a prosthetic left hip, in which case measurements are from the right femur. To accommodate differences in how femoral neck axis length is defined in the Hologic (line A-B in Figure 1 below) and GE-Lunar systems (line A-C in Figure 1) a manual adjustment was made to

the Lunar scans prior to analysis. Specifically, a trained technician moved the axis length line so it ended at point B.

Figure 1**: *Geometry of the Femoral Neck: AB is the femoral neck axis length and DE is the femoral neck width*.**



Body height and weight were measured on every participant, using standard protocols, as part of the Biomarker Project (B4P1A, B4P1B respectively).

Composite indices of femoral neck strength relative to load during a fall were created as follows

Compression strength index (CSI) = BMD*FNW***/**weight

Bending strength index (BSI) = BMD*$(FNW)^2$ ***/***(FNAL*weight)

Impact strength index (ISI) = BMD*FNW*FNAL ***/***(height*weight)

CSI reflects the ability of the femoral neck to withstand an axial compressive load proportional to body weight, BSI reflects the ability to withstand bending forces proportional to body weight, and ISI reflects the ability of the femoral neck to absorb the potential energy of impact in a fall from standing height, regardless of the failure mode: bending or compression. While CSI and BSI assume only that forces on the bone are proportional to body weight, ISI accounts for differences in the forces in a fall that result from differences in a person's height.

The raw BMD data were in units of gms/cm^2 and FNAL and FNW in units of mm. All three composite indices were appropriately scaled so that the final data for the indices are in units of gms/kg-meter.

Naming convention
All variable names start with **B4DFN**
- **B4** denotes Wave 2, Project 4 (per MIDUS naming convention)
- **D** is the code letter assigned to DXA-derived data
- **FN** denotes femoral neck, since all the variables are for the femoral neck

The remaining digits of the variable names indicate the measures described. Three variables representing the femoral neck data obtained from analysis of scans via Hologic software described above and one set of composite strength indices are provided per participant.

The data file contains the following 6 variables for each participant:

B4DFNMW	Femoral Neck minimal neck width (mm)
B4DFNAL	Femoral Neck axis length (mm)
B4DFNBMD	Femoral Neck bone mineral density (gms/cm**2)
B4DFNCSI	Compression Strength Index g/kg-m
B4DFNBSI	Bending Strength Index g/kg-m
B4DFNISI	Impact Strength Index g/kg-m

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