DOCUMENTATION

for

MUSCULOSKELETAL HEALTH and FUNCTION DATA

in

MIDUS 2

BIOMARKER PROJECT

(P4)

University of Wisconsin ♦ Institute on Aging
March 2024

INTRODUCTION

This document provides an overview of the musculoskeletal health and function data collected in the MIDUS 2 (M2) 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 musculoskeletal health measures and also provides comprehensive information regarding methods used to collect the data. Administrative and computed variables are also identified and information about the construction andusage of these variables is included.

Data users are also encouraged to review the 'M2 P4 Biomarker Project Data File Notes'. It provides information about naming conventions, as well as administrative and filter variables included in the data file. The Readme 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 Biomarker data. If there are suggestions or comments, please submit a message through the MIDUS HelpDesk (http://midus.wisc.edu/helpdesk.php).

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SECTION A: OVERVIEW OF DATA FILE AND COLLECTION PROTOCOLS

The Biomarker Project (P4) includes multiple types of data regarding musculoskeletal health (from the indicated sources):

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

As described in the "M2 P4 Biomarker Project Data File Notes" the MIDUS naming convention organizes variables according to data type or the method used for data collection. We have followed this convention with respect to the musculoskeletal health data, thus researchers using bone turnover, DXA, and questionnaire data will need to pull variables from different sections of the data file. See below for brief guidance on where each kind of bone data is located in the data file.

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/musculoskeletal health protocol, as well as additionaldetails about the measures.

REVISION IN THE 2024 UPDATE RELEASE

For lunar femur scan data, when data for both sides were available, we previously computed a set of combined values using the lowest score (from either left or right). In this update release, we included the data from both sides, and removed the computed one side data.

DATA COLLECTION TIMELINE

In contrast to other aspects of the Biomarker data collection, the comprehensiveness of bonehealth 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 NationalInstitute on Aging. The Bone Densitometry Scan Protocol was expanded to all three 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 MIDUS BioCore Lab, so these variables can be found with the other blood assay result data. Details about the blood collection and processing protocols can be found in the "M2 P4 Blood-Urine-Saliva Data documentation."

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 clinicvisit. A copy of the questionnaire appears in Section B 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 they are included in the updated aggregate file. The protocols for both the bone densitometry and whole body scans appear in Section C 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 providing quality control and analyzing scans from all sites.
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 Lunarsystem. 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.

IMPORTANT Analysis Notes: 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. Given these differences, the standard in the field is that BMD values from the two systems are not combined as a variable, but instead T-scores are used in analyses utilizing bone density scan data obtained from both systems. 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." *Journal of Bone and Mineral Research* 27(10):2208-2216.

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-
        i. BMD for the Trochanter and Neck regions as well as Total Femur
        ii. T-score for Neck and Total Femur
    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 agiven case.
- B4DNARSN – categorical variable linked to B4DAVAIL indicating the reason for partialor missing bone density data.
    - Scheduling Problem – scan could not be scheduled due to the respondent's travel schedule.
    - Technical Problem – scan not done due to technical difficulties/problems at thetime of the scan.
    - Scan Not Scoreable – scan was done but could not be scored. This occurredmost often due to the presence of metal rods in the bone.
    - Visit Terminated- clinic visit was terminated due to acute respondent healthproblems.
    - 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 bonedensitometry scans were available at the site (B4DAVAIL=9).
- B4DSTYPE - The scanner system (Lunar, Hologic) used to collect the data.
- B4DRSIDE - Region specific variables indicating the side (left or right) scanned for the radius.
    - - 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 heightor 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 asimple 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]		

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 recreationalsports 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), eitherat 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 andyou 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 thelawn 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 inregular 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 thestart 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 variability7 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 yourbody. [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

CONTACT INFORMATION

DXA/IQC Related Issues:	1. Diane Krueger University of Wisconsin-Madison 2870 University Ave. Suite 100 Madison, WI 53705 Phone: 608-265-6410 Fax: 608-265-6409 Email: dckruege@wisc.edu 2. Gretta Borchardt University of Wisconsin-Madison 2870 University Ave. Suite 100 Madison, WI 53705 Phone: 608-265-6410 Fax: 608-265-6409 Email: gborchardt@wisc.edu
Study Specific Protocol Issues:	1. MIDUS HelpDesk http://midus.wisc.edu/helpdesk.php

DXA OPERATOR'S SIGN-OFF

This is to insure that all DXA technologists have read and fully understand what will be expected from their site for the DXA 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 Diane Krueger at 608-265-6409. 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, 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 QA Center of all hardware issues or replacements
  4. Notify UW DXA QA Center of all software problems or upgrades

- Ensure that DXA measurements are skillfully and consistently acquired for each subject, following the procedures in the manufacturer's operator's manual and this manual.
  1. Demographic entry
  2. Scan modes
  3. Positioning and acquisition
  4. Data back-up and archival

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

UW Osteoporosis Research DXA QA Center

- Monitor the performance of all densitometers used for DXA acquisition 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 QA and study data in a timely manner

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

- Assure that study sites have proper supplies needed for DXA data transmission
  1. Study specific DXA 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 cannotstart 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. Youwill 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 subjects 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: Spine or Whole Body as appropriate
MIDDLE INITIAL: Leave blank
ETHNICITY: White
SEX: F
BIRTHDATE: 11/11/1951
PATIENT ID: Leave blank
IDENTIFIER 2: Site location (e.g. UW, UCLA, and 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 becorrect 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 thatpatients 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 forinstructions. 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 analyzingphantom 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 onthree 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 scan 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 yourecalculate 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 theGCRC 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. Pleasefill 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 specificmode.

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 isvisualized. 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 andthe 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 asgauge
- 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 until toes touch, and 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 RIGHTARM. 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 tothe 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 thebone 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 [Burgeet al. 2007]. The major predictor of hip fracture risk is the 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, thoughimportant, 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 bothmaterial density and structure size.

To keep fracture risk low, the strength of the femoral neck needs to be high relative to the forcesthat 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.

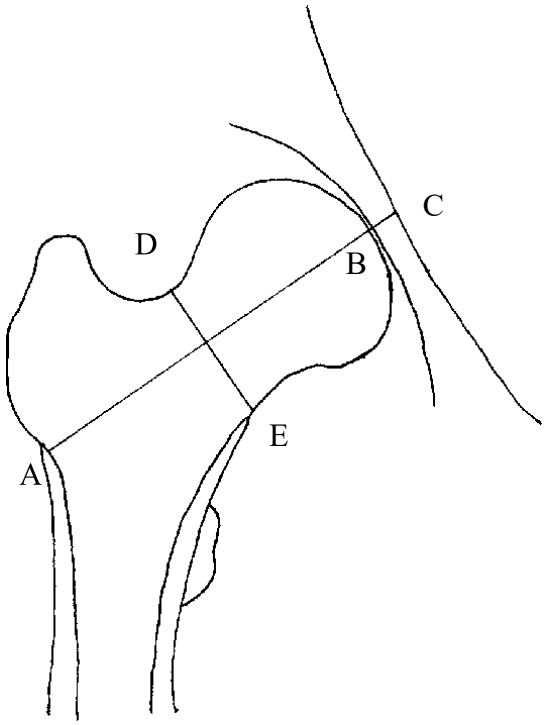
1. Femoral neck axis length (FNAL): the distance along the long axis of the femoral neckfrom the lateral margin of the base of the greater trochanter to the apex of the femoralhead (line A-B in Figure 1)
2. Femoral neck width (FNW): the smallest thickness of the femoral neck along any lineperpendicular 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, UCLAand 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 lineso it ended at point B.

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



Body height and weight were measured on every participant, using standard protocols, as partof 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 tobody weight, BSI reflects the ability to withstand bending forces proportional to body weight, andISI 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 variablesrepresenting 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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