MIDUS REFRESHER BIOMARKER PROJECT OVERVIEW

The Biomarker Project is one of multiple projects comprising the MIDUS Refresher "Integrative Pathways to Health and Illness" study. For the past two decades, the overarching objective of MIDUS has been to investigate linkages between sociodemographic, psychosocial, behavioral, and neurobiological variables to account for unfolding profiles of morbidity and mortality across the decades of adult life as well as the maintenance of good health and functional capacities. The study has facilitated analyses that pay attention simultaneously to age, gender, race, and socioeconomic variation in how psychosocial and neurobiological variables are linked. In addition, the Refresher sample will permit assessment of the impact of the ongoing economic recession on the health of diverse-aged adults via comparison with the extant Biomarker data from the MIDUS 2 sample. It will also lay the foundation for parallel longitudinal studies of same-aged adults from different birth cohorts on whom unfolding health trajectories are studied as the product of interacting domains of influence (biological, psychological, social) in a changing historical context (economic recession).

The Refresher Biomarker Project (P4) supported this goal primarily through assessment of a variety of biological indicators of physiology and health according to the basic protocol implemented at MIDUS 2. The protocol also included assessments of additional aspects of psychosocial experience. Modifications to that basic protocol and psychosocial assessments are noted below as appropriate. Data was collected during a 24-hour stay at one of 3 Clinical Research Units (CRU). The following provides basic information about the sample, recruitment, and data collection procedures. Additional information about the basic assessments and the MIDUS Core Biomarker sample (i.e. MIDUS 2) can be found in:

> Love, G.D., Seeman, T.E., Weinstein, M., & Ryff, C.D.. (2010). Bioindicators in the MIDUS National Study: Protocol, Measures, Sample and Comparative Context. *Journal of Aging and Health*.

The Sample

MIDUS participants were eligible for Biomarker data collection if they:

- Completed the MIDUS Refresher Survey Project Phone Interview and Self-Administered Questionnaire **OR** Completed the Milwaukee Refresher survey project in-person CAPI interview and Self-Administered Questionnaire
- Lived in the continental U.S.

Eligible participants were assigned to one of the three P4 data collection sites (University of California Los Angeles (UCLA)/Site 1, University of Wisconsin (UW)/Site 2 or Georgetown University (GU)/Site 3) based on the region (West Coast, Midwest, and East Coast, respectively) in which they lived.

Recruitment

Recruitment was a two-step process. Staff at a given data collection site sent a recruitment packet (letter and brochure describing the study) to individuals assigned to their site. Within a few

weeks, designated staff at that site made a follow-up call to answer any questions the individual may have had, then attempted to schedule a CRU visit and facilitated travel arrangements.

Informed Consent

Verbal consent is obtained by phone when individuals agree to participate and schedule a CRU visit. Written consent is obtained at the clinic prior to beginning study procedures.

Data Collection Procedures

All biomarker assessments, with the exception of sleep assessments, were completed during the overnight stay at the regional CRU. The protocol for the visit was standardized across the three sites so that assessments were completed as follows:

Day 1 (late afternoon or evening of the day the person arrived at the CRU)

- Medication Chart
- Medical History
- Self-Administered Questionnaire (SAQ)
- Pittsburgh Sleep Questionnaire (PSQ)
- Physical Exam (Vitals)
- 12-hour Urine Collection began

Day 2 (the morning of the day the person left the CRU)

- 12-hour Urine Collection ended
- Fasting Blood Draw
- Psychophysiology Experimental Protocol
- Physical Exam (Functional Assessments)

The following assessments could be completed on Day 1 or Day 2 to provide flexibility in accommodating availability of clinical staff:

- Bone and muscle function (Densitometry (DXA) Scan, Jump/Balance) as well as Gait assessments. These assessments are done at UW only.
- The Ankle Brachial Index Assessments (ABI). These assessments were done at UCLA only.

Methods for collecting psychosocial data are described below, followed by the protocols for collecting biomarker data.

Psychosocial Assessments

Psychosocial experience was assessed using the SAQ, PSQ and sections of the Medical History. Psychometric information and details about the scales included in the SAQ and PSQ can be found in the Documentation for Psychosocial Constructs and Composite Variables. Key sections and details about each instrument are highlighted below.

Self-Administered Questionnaire (SAQ)

The 25-page SAQ booklet is available as a standalone file with the other biomarker documentation and contains the following scales:

MASQ (Mood and Symptom Questionnaire
Overall Assessment of day
CES-D (Center for Epidemiologic Studies- Depression)
Perceived Stress Scale
Spielberger Anger Expression
Spielberger Trait Anger
Spielberger Trait Anxiety
Social Anxiety
Childhood Trauma Questionnaire (CTQ)
Positive Events Scale
Singelis Self-Construal Scale
Social Obligation Scale
Relational-Interdependent Self Construal (RISC)
Sympathy Scale
Adjustment Scale
Support/Strain Given to Others
Self-Control
Minimalist Wellbeing
Subjective Well-Being
UCLA Loneliness Scale

Pittsburgh Sleep Questionnaire (PSQ)

The PSQ is a 2-page document. It includes a few questions that were to be answered by the participant's bed partner or roommate. Thus, it was mailed to the respondent with the visit confirmation packet for completion prior to his/her arrival at the CRU. A copy of the instrument can be found in the documentation for Sleep Data, along with details about collection of physiological sleep data (see below).

Medical History

Although most of this instrument assesses aspects of the respondents' medical and health conditions/behaviors (see below), the final three sections were used to identify significant life events the participant may have experienced since completing the Phone Interview component of the Survey project. These assessments include questions about:

- Changes in marital status
- Deaths of family members and/or close friends
- Other significant life events, positive or negative, that the respondent chose to tell us about

The Medical History is administered as a computer assisted personal interview (CAPI). A Word version of the instrument, including SVNs (Short Variable Names) was exported from the CAPI software. It is available as a standalone PDF with the other biomarker documentation.

Biomarker Assessments

Medical History

In addition to the life event assessments mentioned above, the Medical History also included assessments of the following:

- Symptoms and Conditions
- Major Health Events (broken bones, surgeries, head injuries, joint injuries, motor vehicle accidents, amputations, other)
- Immune Function: Allergies and Immunizations (childhood & adult)
- Family Medical History
- Current Health Practices: Diet, Exercise, Smoking, Alcohol, Health Care and Screening

At MIDUS 2, a separate short interview was also administered to assess history of broken bones and falls, as well as other health behaviors/experiences that might affect bone health. That set of items has been integrated into the Refresher Medical History interview, thus it now also includes the following assessments.

- History of broken bones and falls for participant and immediate family (Q3-5)
- Medical conditions that might impact bone health (Q6)
- Medication/Treatment History – use of osteoporosis medication (Q7) and other medications or treatments (e.g. chemotherapy) that could affect bone health (Q8)
- History of smoking, passive smoking (Q37-48), and exercise (Q31-35)
- Women's Health – number of past pregnancies, current menarchal status (e.g. pre or post-menopausal) (Q62-69)
- Metal in the body – provides information about pins, rods, and other metal in the body to facilitate interpretation of whole body scan data (Q76-80)

Physical Exam: Short Version

The short version of the physical exam was completed at all 3 sites following standardized procedures. It included the following assessments:

- Vital Signs: Height, weight, pulse, blood pressure, respiration, and temperature
- Waist & Hip (maximum extension & iliac crest) Measurement
- Functional Assessments: grip strength, visual acuity, peak flow, 50-foot timed walk, and chair stands

Physical Exam: Long Version (UW Only)

The long version of the physical exam was conducted only at Site 2 due to the availability of clinical staff (physicians and nurse practitioners) able to complete this assessment. It was designed to parallel basic assessments completed as part of a comprehensive but non-invasive physical exam. It included assessments of the following:

- Integument (hair, skin)
- Hearing (hearing, bone conduction, pinnae, external canal, ear drum)
- Sinuses

- Mouth (#of teeth, cavities, alignment, torus, etc.)
- Neck (range of motion, tenderness, thyroid)
- Cardiovascular (auscultation, murmurs, pulses)
- Thorax and Lungs (inspection, auscultation)
- Musculoskeletal (muscles, spine, joints, tender points, extremities)
- Neurological (coordination, motor system, reflexes, sensation, autonomic)

Details about the protocol for conducting the short and long physical exams can be found in the Physical Exam Data documentation.

Medication Data

Study participants were asked to bring all of their prescription, over the counter, and alternative medications to the CRU. Data about these medications was recorded on a 3-page form. One page was for prescription medications and one for over-the counter medications. The third page included a section for alternative medications and a section for recording information about medication allergies. The following information was recorded for each type of medication:

- Medication Name
- Dosage
- Route by which it is administered (e.g. by mouth, topical, etc.)
- Frequency
- How long the participant has been taking it
- Why the participant thinks s/he is taking the medication

The CRU's require that information about medications to be taken during the visit be available prior to the participant's arrival. Thus, the above information was obtained or confirmed at the time of the visit.

Details about medication data collection and coding can be found in the Medication Data documentation. This document also includes details about therapeutic and pharmacologic class codes that are attached to the medication data via linkage to the Lexi-Data Database®. This document also provides details about assigning modified ICD-9 and ICD-10 codes (International Classification of Diseases, version 9 and 10) and a set of MIDUS specific codes to the reasons for taking medications reported by participants.

Musculoskeletal Health Data

Musculoskeletal health was assessed via a questionnaire (see Medical History above), DXA (Dual X-Ray Absorptiometry) scan, muscle function assessments, and assays for select blood based biomarkers. Blood samples for biomarker assay were collected at all sites for all participants and are described, separately, below.

Bone densitometry and DXA based body composition data, as well as muscle function (jump/balance) data are obtained only at Site 2 (UW) do to funding limitations. In addition, 2 sites (UW, UCLA) also obtained body impedance data via different methods. Details about these protocols and data can be found in the Musculoskeletal Health Data documentation.

Ankle Brachial Index (ABI)

Ankle Brachial Index is measured using the Summit Doppler Vantage ABI™ system via blood pressure cuffs placed in four locations while the participant is lying down. At the end of a 5-minute resting period, the four cuffs are activated in rotation (right arm, right ankle, left arm, left ankle) with the device automatically inflating the cuff, measuring systolic pressure and deflating the cuff. ABI is the ratio of systolic blood pressure in the arteries (typically measured at the ankle) to the brachial (upper arm) systolic blood pressure

The ABI assessment was added to the MIDUS Biomarker Refresher protocol as a pilot project conducted only at Site 1 (UCLA). It was added because ABI can be an indication of peripheral vascular disease. Details about this procedure can be found in the Ankle Brachial Index documentation.

Tissue Sample (Blood, Urine, Saliva) Assays

A 12-hour urine sample and fasting blood samples were collected from each participant. To ensure consistency, all samples were collected and processed at the CRU, using standardized procedures and then fresh and frozen samples were shipped to the MIDUS BioCore Lab for assay as follows:

- Fresh whole blood sample was sent weekly and assayed for:
  - Hemoglobin A1c
- Frozen Serum in 2 ml aliquots were shipped monthly
  - Cholesterol Panel (Total, HDL, and LDL) and Triglycerides
  - Glucose metabolism marker - Insulin, Glucose, Insulin-like Growth Factor (IGF-1)
  - Hormone markers - DHEA and DHEA-S
  - Inflammation markers -IL-6, s-IL6-r, IL-8, IL-10, TNF-alpha, C-Reactive Protein, Fibrinogen, E-Selectin, ICAM
  - Anti-Oxidants - *trans*-beta-carotene, 13-*cis*-beta-carotene, alpha-carotene, cryptoxanthin, lutein (*cis, trans,* total), zeaxanthin, lycopene (*13-cis, 9-cis, trans*, total), retinol, alpha-tocopherol, gamma-tocopherol
  - Bone Turnover – BSAP (Bone Specific Alkaline Phosphatase), NTx (n-teleopeptide type 1 collagen), P1NP (aminoterminal propeptide type 1 procollagen)
  - Creatinine
- Frozen Urine 11 ml aliquots were shipped monthly
  - Catecholamines – epinephrine, norepinephrine, dopamine
  - Cortisol
- Frozen Saliva samples were shipped monthly and assayed for Cortisol
- Stored serum samples were assayed in 2023 for suPAR
- Stored urine samples were assayed in 2023 for Albumin and Cystatin C

Details about tissue sample collection and biomarker assays can be found in the Blood, Urine and Saliva Data documentation.

PsychoPhysiology Experimental Protocol

The protocol included two 6-minute cognitive challenges, followed by a 6-minute orthostatic (standing) challenge. Physiological reactivity during the challenge tests was monitored via measures of: 1) heart rate variability and respiration, providing an index of central-peripheral neural feedback and central nervous system-autonomic nervous system integration; 2) beat-to-beat blood pressure; and 3) Collection of 5 saliva samples over time (session start, baseline, 6 minutes after the second mental challenge, 6 minutes after the end of the physical challenge, and 30 minutes after the session) for cortisol assay.

Details about this protocol can be found in the Psychophysiology Protocol documentation.

Sleep Efficiency (UW/Site 2 only)

Physiological measures of sleep were assessed only at Site 2. Participants at this site were asked to wear the Actiwatch continuously for 7 days. The data collection period was standardized to begin on the Tuesday following the day the participant arrived home after completing the CRU visit. Data collection ended a week later on the following Tuesday morning. The Actiwatch is a lightweight, watch-sized, waterproof, activity monitoring device that was worn on the wrist. Participants were also asked to complete a paper and pencil daily sleep diary during the period that the Actiwatch was worn. These materials are mailed back to UW at the end of the data collection period.

The Daily Sleep Diary included assessments of daily:

- Daytime naps, exercise, caffeine and alcohol consumption, and use of sleep aids as well as other medications that were not taken on a daily basis
- Subjective Sleep Quality – time to bed, time to rise, sleep disturbance, ratings of sleep quality

Details about sleep assessments and a copy of the Daily Sleep Diary can be found in the Sleep Data documentation.