MIDUS 2 BIOMARKER PROJECT OVERVIEW

The Biomarker Project is one of multiple projects that comprise the MIDUS 2 "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.

The M2 Biomarker Project (P4) includes assessment of multiple indicators of physiological regulation/dysregulation and health. Data were collected during a 24-hour stay at one of three Clinical Research Units (CRU). The following provides basic information about the sample, recruitment, and data collection procedures. Additional information about 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, 22, 1059-1080*.

The Sample

MIDUS participants were eligible for Biomarker data collection if they:

- Completed the MIDUS 2 Survey project Phone Interview and Self-Administered Questionnaire **OR** Completed the Milwaukee 1 survey project in-person CAPI interview and Self-Administered Questionnaire
- Were in the MainRDD (not including city oversamples), Twin or African American samples
- 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, 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 General Clinical Research Center (GCRC) visit and facilitated travel arrangements.

Informed Consent

Verbal consent is obtained when individuals agree to participate and schedule a GCRC 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 GCRC. 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 GCRC)

- Medication Chart
- Medical History
- Self-Administered Questionnaire (SAQ)
- Pittsburgh Sleep Questionnaire (PSQ)
- Physical Exam Long Version (Midwest Site 2 Only)
- 12-hour Urine Collection began

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

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

Bone Assessments (Questionnaire & Densitometry Scan) were completed on Day 1 or Day 2

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 documentations 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
Having a Good Life in America

Pittsburgh Sleep Questionnaire (PSQ)
The PSQ is a 2-page document. A copy of the instrument can be found in the Sleep Data documentation. 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 GCRC.

Medical History
Although most of this instrument assesses aspects of the respondents' medical and health behaviors (see below), the final three pages (22-24) were used to identify significant life events the participant may have experienced since completing the Project 1 Phone Interview. 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 25-page Medical History booklet is available as a standalone file with the other biomarker documentations.

Biomarker Assessments

Biomarker assessments include objective and subjective measures obtained via multiple methods ranging from a medical history interview to clinical measurements to an experimental protocol. Key elements of each are described below.

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, and other)
- Immune Function: Allergies and Immunizations (childhood and adult)
- Family Medical History
- Current Health Practices: Diet, Exercise, Smoking, Alcohol, Health Care and Screening

Summary variables are created for some of the Medical History items, see the Documentation for Psychosocial Constructs and Composite Variables for details.

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) Measurements
- 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 and skin)
- Hearing (hearing, bone conduction, pinnae, external canal, and ear drum)
- Sinuses
- Mouth (number of teeth, cavities, alignment, torus, etc.)
- Neck (range of motion, tenderness, and thyroid)
- Cardiovascular (auscultation, murmurs, and pulses)
- Thorax and Lungs (inspection and auscultation)
- Musculoskeletal (muscles, spine, joints, tender points, and extremities)
- Neurological (coordination, motor system, reflexes, sensation, and autonomic)

Details about the protocol for conducting the short and long physical exams can be found in the Physical Exam Data documentation. Additional details about some variables may be found in the Biomarker Project Data File Notes.

Medication Data

Study participants were asked to bring all of their prescription, over the counter, and alternative medications to the GCRC. 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

Some GCRC's required information about medications to be taken during the visit prior to the participant's arrival. Thus, the above information was obtained or confirmed at the time of the visit.

The following details about medication data can be found in the Medication Data documentation:

- Data collection and processing
- Therapeutic and pharmacologic class codes that are attached to the medication data via linkage to the Lexicomp® Lexi-Data database

- Assigning modified ICD-9 and ICD-10 codes (International Classification of Diseases, version 9 and version 10) and a set of MIDUS specific codes to the reasons for taking medications reported by participants

Bone Health Data

Bone health was assessed via a questionnaire, bone densitometry scan, and assays for select blood based biomarkers. Blood samples for biomarker assay were collected at all sites for all participants and are described below. Site 2 (UW) added bone densitometry scans to the protocol in September 2004. Site 3 (Georgetown) and Site 1 (UCLA) added bone densitometry to their protocols in April 2006 and February 2006, respectively. The Bone Questionnaire was developed in late summer 2005. The UW site began administering the questionnaire at that time, and the other two sites began using it when they began conducting bone densitometry scans. A whole body scan was added to the densitometry scan protocol in 2007.

The Bone Questionnaire was administered by project staff at the same time as the Medical History, it assessed the following:

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

The bone densitometry protocol included scans of the lumbar spine and the femur. Site 2 (UW) used the Lunar scanning system, while the other two sites used the Hologic scanning system.

Details about these protocols and data can be found in the Musculoskeletal Health Data documentation.

Tissue Sample (Blood, Urine) 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 GCRC 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
  - Hormone markers - DHEA and DHEA-S
  - Inflammation markers -IL-6, s-IL6-r, 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), and P1NP (aminoterminal propeptide type 1 procollagen)
    - Creatinine
- Frozen Urine 15 ml aliquots were shipped monthly
    - Catecholamines- epinephrine, norepinephrine, and dopamine
    - Cortisol
- Stored serum samples were assayed in the Summer 2010 for Insulin, Glucose, and Insulin-like Growth Factor 1 (IGF-1)
- 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:

- Heart rate variability and respiration, providing an index of central-peripheral neural feedback and central nervous system-autonomic nervous system integration
- Saliva cortisol assessments at 4 time points (baseline, 6 minutes after the second mental challenge, 6 minutes after the end of the physical challenge, and 30 minutes after the session)
- Beat-to-beat blood pressure measured continuously throughout the protocol

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-64 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 GCRC visit. Data collection ended the following Tuesday morning. The Actiwatch-64 is a lightweight, watch-sized, water proof, and 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, and ratings of sleep quality

Details about sleep assessments can be found in the Sleep Data documentation.