

White Paper: Biomarker-Based Validation of Diet and Physical Activity Assessment Tools in Existing Cohorts

Background: Data from NCI's Observing Protein and Energy Nutrition (OPEN) study and the Women's Health Initiative have provided critical information on the extent and structure of measurement error in commonly used dietary instruments---the food frequency questionnaire (FFQ), 24-hour recall, and food record. The inclusion of doubly labeled water (DLW) in these studies permitted accurate assessment of misreporting on an FFQ and its effect on estimated relative risks (RRs) in epidemiologic studies. The use of activity monitors in the 2003-06 National Health and Nutrition Examination Survey indicated significant disagreement between self-reported activity and objective data. These measurement error results call into question the null results from large cohort studies and pooled analyses of cohort studies and raise the possibility that even observed associations underestimate true effects. The development of new diet and physical activity assessment tools and the importance and relevance of these large recovery biomarker studies suggest a need for replication of the findings, assessment of new instruments, and incorporation of more accurate measures of energy expenditure. A limitation of most large biomarker studies to date is a focus on dietary measurement error. The burgeoning epidemic of obesity highlights the need to explore measurement error in both aspects of energy balance--dietary intake and energy expenditure through physical activity. A key question is whether dietary and physical activity measurement errors are influenced by weight status.

Purpose: A number of critical gaps remain in our overall understanding of the measurement error problem in diet and physical activity assessment. A multidisciplinary team of experts at NCI have identified these scientific gaps and have provided an example study design for external researchers in this field to consider when proposing studies in this arena.

Sample Study Aims:

1. Replicate and expand dietary measurement error findings demonstrated in OPEN and WHI studies in the following three ways:
 - a. Utilize other FFQs and reference dietary instruments including a new NCI-developed web-based automated self-administered 24-hour dietary recalls(ASA24) as well as dietary records/diaries to assess whether such instruments should be used instead of or in conjunction with FFQs as the primary assessment tools in prospective cohort studies
 - b. Determine whether measurement error findings vary among different study populations.
 - c. Analyze biologic samples for metabolomic profiles of nutritional exposure
2. Investigate the measurement error structure associated with multiple measures of physical activity (objective monitors, questionnaires, a new NCI-developed web-based automated self-administered 24-hour activity questionnaires [ACT24]) using

biomarkers of physical activity energy expenditure (PAEE), where $PAEE = DLW \text{ Total Energy Expenditure} - (\text{Resting Metabolic Rate (RMR)} + \text{Thermic Effect of Food})$.

3. Evaluate alternative methods for combining objective and self-report assessment data, from the perspective of minimizing diet and physical activity measurement error.
4. Within the context of a cohort study, evaluate alternative methods for adjusting observed relative risks for the measurement error determined from the biomarker calibration study. These measurement error adjustment methods should be applied to several diet/physical activity-chronic disease hypotheses.
5. Evaluate the potential for 'energy adjustment' that incorporates physical activity and body size.

Such studies would be the first to incorporate biologic and questionnaire measures of energy intake and expenditures as well as objective measures of physical activity. Evaluation of the interrelations among these measures of energy balance will provide critical insights into advancing our ability to assess energy–cancer relations and the determinants of obesity.

Design: Studies will be conducted within ongoing prospective cohort studies with existing extensive dietary and physical activity data. Cohorts of particular interest include those that would provide multiple racial/ethnic groups, diverse dietary and physical activity instruments, a wide range of dietary intakes, and a wide weight distribution. Individual studies in this arena are anticipated to be a highly collaborative project in which data could be pooled to gain the power necessary for analyses of measurement error.

Studies should utilize cohorts that have already collected FFQ data on total diet and physical activity questionnaire (PAQ) data on participants (750 men and 750 women per cohort, or 750 respondents per single-gender cohort). Studies should provide a wide range of dietary intake (for several key foods and nutrients) and physical activity data among their participants. Participant access to broad-band internet is essential. Studies should have access to clinical facilities for the biomarker studies and capability to conduct the study within a two year period. Figures 1-3 provide information about the overall study design and timeline, including the allocation of participants in each site into four study groups. The study will assess energy and protein intakes using unbiased 'reference' biomarkers, and compare them to two administrations of FFQs and other dietary report 'reference' instruments including 24-hour dietary recalls, food records/diaries, and blended instruments (for example, FFQ and recalls or checklist) – each administered in each season across study groups over a one year period. For physical activity energy expenditure, the study will use DLW to measure total energy expenditure and indirect calorimetry to measure resting metabolic rate (RMR). Data collection will be conducted such that one-quarter of participants in each cohort will be dosed with DLW and have RMR measured in each season. A substudy should be conducted in a sample of 50 respondents in each study site to repeat both the DLW dose (for total energy expenditure) and RMR measure six months apart to assess within person random error in these variables. (Note: DLW isotopes and physical activity monitors

will be purchased and provided by NCI.) For protein, the study should include eight, 24-hour urine collections (for urinary nitrogen) -- two per season a few weeks apart. Urine collections should include the use of the para-amino benzoic acid (PABA)-check to assess completeness of urinary collections. In addition, proposed studies should collect PAQs, web-based 24-hour activity questionnaires and objective measures of physical activity (specific device to be used across sites to be determined) as well as body composition data (DEXA). Blood should be collected and stored. Height, weight, and circumferences (anthropometry) at several body sites should be measured in each respondent in each season.

The size of this study will likely necessitate multiple labs to conduct analyzes such as those for DLW, urinary nitrogen, urinary PABA, metabolomic profiles, or other nutrient biomarkers within the required time-frame. Therefore, participating labs may need to work together to establish standardized protocols to assure comparable biomarker results across multiple cohort studies.

Power calculations indicate that this sample study design will have approximately 85% power to test, within each cohort and gender, the null hypothesis that the attenuation factor (a measure of relative risk attenuation due to measurement error in diet-disease studies) for ASA24-reported or FFQ-reported energy-adjusted protein is greater than 0.5, versus the alternative hypothesis that it is 0.4 or less. The hypotheses are based on an analysis of the OPEN study which estimated that the attenuation factor for six 24-hour recalls is greater than 0.5 (both men and women), while the attenuation factor for an FFQ was between 0.35 (women) and 0.4 (men). The study will also have approximately 85% power to test for heterogeneity of attenuation factors across studies by testing the null hypothesis that the standard deviation in attenuation factors is 0, versus the alternative hypothesis that it is 0.075 or greater.

Scientific Rationale: NCI has long conducted and sponsored research in nutrition and cancer. Animal experiments, first carried out in carcinogen-induced and more recently in transgenic models, have demonstrated conclusively that nutritional change—energy restriction as well as alteration of specific macro- and micronutrients--can modulate tumorigenesis in mammals. Observational epidemiologic studies have consistently shown elevated risks in relation to overweight and obesity for several cancer sites, including breast, colorectum, endometrium, kidney, esophageal adenocarcinoma, etc. The recent World Cancer Research Fund/American Institute for Cancer Research report on "Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective cited obesity as a 'convincing' cause of malignancy for several cancer sites, while physical activity was determined to be protective for many cancers. Such data and conclusions make it imperative that the assessment of dietary intake and physical activity be understood, improved, and accurately characterized.

With respect to intake of energy and other nutrients/dietary constituents, such progress is particularly important given that the epidemiologic evidence for a diet and cancer association in humans is unclear. International correlation studies and pooled results from some case-control studies suggest an important, albeit moderate, association

between several dietary factors and major cancers. Several large prospective studies, however, have challenged this conventional wisdom in reporting no associations between, for example, dietary fat and breast cancer, dietary fiber and colorectal cancer, and, most recently, fruit and vegetable intake and colorectal cancer.

These null epidemiologic findings may ultimately be shown to be correct. Alternatively, however, the studies themselves may have serious deficiencies due to the underappreciated effect of measurement error in dietary exposure assessment instruments (primarily FFQs). These deficiencies could be obscuring real nutrition-cancer links and misleading investigators with respect to assessing outcomes related to obesity and cancer. The concern about FFQs is evidenced by the fact that several prominent groups around the world are considering using food records/diaries as the primary dietary assessment tool in prospective cohort studies. However, no study has yet been done to firmly establish that the attenuation in relative risks associated with records/diaries is significantly less than that for FFQs. The current study would be able to assess the extent of measurement error, with respect to energy and protein, with the inclusion of unbiased biomarkers of intake.

The consistent body of epidemiologic evidence implicates physical inactivity in the etiology of colorectal and other cancers among other chronic diseases. Concern persists, however, that the true risks for physical inactivity are understated due to the imprecision of self-reported assessment instruments. Obtaining accurate physical activity measures is essential to understand chronic disease and physical activity links. The current study will be the most comprehensive to date in comparing physical activity measures, both self-reported and objective, to physical activity energy expenditure measured by biomarker and calorimetry. These data will facilitate advances in accounting for physical activity measurement error and correcting for it.

In summary, the considerable uncertainty about the structure of dietary and physical activity measurement error presents a serious challenge to our research efforts to assess links between energy balance, diet and cancer. Such error may lead us to miss important diet- and physical activity-related cancer connections and thereby fail to grasp the extent to which energy intake, dietary change, and increased physical activity could alleviate the burden of malignant disease.

FIGURE 1: OVERALL STUDY DESIGN AND TIMELINE

Biomarker-Based Validation of Diet and Physical Activity Assessment Tools in Existing Cohorts – 12 months

Groups 1 to 4 = ¼ of the study sample

A and B = half of the study sample, designates order effect of Food Record with 24-hr recall

Months 1-3	Months 4-6	Months 7-9	Months 10-12
Study-specific FFQ1 (baseline, Groups 1-4) Checklist1 (baseline, Groups 1-4))			Study-specific FFQ2 (at completion, Groups 1-4) Checklist2 (at completion, Groups 1-4))
Anthropometry (Groups 1-4) 2 Urine (Groups 1-4) 24-Hour Recall- ASA24 (Groups 1-4) 24-Hour Activity Recall- ACT24 (Groups 1-4)	Anthropometry (Groups 1-4) 2 Urine (Groups 1-4) 24-Hour Recall- ASA24 (Groups 1-4) 24-Hour Activity Recall- ACT24 (Groups 1-4)	Anthropometry (Groups 1-4) 2 Urine (Groups 1-4) 24-Hour Recall- ASA24 (Groups 1-4) 24-Hour Activity Recall- ACT24 (Groups 1-4)	Anthropometry (Groups 1-4) 2 Urine (Groups 1-4) 24-Hour Recall- ASA24 (Groups 1-4) 24-Hour Activity Recall- ACT24 (Groups 1-4)
DLW (Group 1) Subset Repeat DLW (Group 3) RMR (Group 1) Subset Repeat RMR (Group 3)	DLW (Group 2) Subset Repeat DLW (Group 4) RMR (Group 2) Subset Repeat RMR (Group 4)	DLW (Group 3) Subset Repeat DLW (Group 1) RMR (Group 3) Subset Repeat RMR (Group 1)	DLW (Group 4) Subset Repeat DLW (Group 2) RMR (Group 4) Subset Repeat RMR (Group 2)
PA monitor (Groups 1, 3) Calibration HRM (Group 1) Food Record1A (Groups 1, 3) Fasting Blood1 (Groups 1, 3) DEXA1 (Groups 1, 3) Study specific PAQ1 (Groups 1, 3)	PA monitor (Groups 2, 4) Calibration HRM (Group 2) Food Record1B (Groups 2,4) Fasting Blood1 (Groups 2,4) DEXA1 (Groups 2,4) Study specific PAQ1(Groups 2,4)	PA monitor (Groups 1, 3) Calibration HRM (Group 3) Food Record2B (Groups 1,3) Fasting Blood2 (Groups 1,3) DEXA2 (Groups 1,3) Study specific PAQ2 (Groups 1,3)	PA monitor (Groups 2, 4) Calibration HRM (Group 4) Food Record2A (Groups 2,4) Fasting Blood2 (Groups 2,4) DEXA2 (Groups 2,4) Study specific PAQ2 (Groups 2,4)

Other Questionnaires – administered during clinic visits, or at Baseline or at end

FIGURE 2: LISTING OF STUDY ACTIVITIES BY FREQUENCY

Biomarker-Based Validation of Diet and Physical Activity Assessment Tools in Existing Cohorts
12-month study

All Participants (subscripts indicate each occurrence of a data collection element):

Once:

- RMR – measured once with DLW,
 - Subset repeat 6 months apart, n=50 per site
- DLW – administered once
 - Subset repeat 6 months apart, n=50 per site
- Individual calibration of PA Monitors, if needed
- Other Questionnaires – Given at baseline or at clinic during DLW testing, etc

Twice:

- Study-specific FFQ₁ – baseline
- Study-specific FFQ₂ – end of study
- Checklist₁ – baseline
- Checklist₂ – end of study
- Fasting bloods (FB) – twice, 6 months apart
- DEXA – twice, 6 months apart
- PA Monitors – twice, 6 months apart, once during DLW period with RMR measure
- Food Records (FR)- twice, 6 month apart, split order with 24-HR (A=After, B=Before, 3-6 weeks apart from each other
- Study-specific Physical Activity Questionnaire (PAQ)- twice, 6 months apart

Four times:

- Anthropometry – each quarter
- 2 Urinary Nitrogen collections (UN) – two in each quarter, 2 weeks apart
- One 24-Hour Dietary Recall – ASA24 - each quarter
- One 24-Hour Activity Recall – ACT24 - each quarter

FIGURE 3: STUDY ACTIVITIES BY STUDY GROUP GROUP 1

Months 1-3

Study-specific FFQ₁ Baseline
Checklist₁ Baseline
Anthropometry₁
2 UN_{1,2}
24-Hour Recall- ASA24₁
24-hr Activity Recall – ACT24₁
RMR
DLW
PA monitor₁ – at first DLW visit
Calibration PA monitor, if needed – at second DLW visit, with RMR
Study-specific PAQ₁ – at second DLW visit
FR_{1A}
Fasting Blood₁
DEXA₁

Months 4-6

Anthropometry₂
2 UN_{3,4}
24-Hour Recall- ASA24₁
24-hr Activity Recall – ACT24₂

Months 7-9

Anthropometry₃
2 UN_{5,6}
24-Hour Recall- ASA24₃
24-hr Activity Recall – ACT24₃
Subset Repeat DLW (n=25/site)
Subset Repeat RMR (n=25/site)
PA monitor₂
Study-specific PAQ₂
FR_{2B}
Fasting Blood₂
DEXA₂

Months 10-12

Anthropometry₄
2 UN_{7,8}
24-Hour Recall- ASA24₄
24-hr Activity Recall – ACT24₄
Study-specific FFQ₂
Checklist₂

GROUP 2

Months 1-3

FFQ₁ Baseline
Checklist₁ Baseline
Anthropometry₁
2 UN_{1,2}
24-Hour Recall- ASA24₁
24-hr Activity Recall – ACT24₁

Months 4-6

Anthropometry₂
2 UN_{3,4}
24-Hour Recall- ASA24₂
24-hr Activity Recall – ACT24₂
DLW
RMR
PA monitor₁ – at first DLW visit
Calibration PA monitor, if needed – at second DLW visit, with RMR
FR_{1B}
Fasting Blood₁
DEXA₁
PAQ₁– at second DLW visit

Months 7-9

Anthropometry₃
2 UN_{5,6}
24-Hour Recall- ASA24₃
24-hr Activity Recall – ACT24₃

Months 10-12

Anthropometry₄
2 UN_{7,8}
24-Hour Recall- ASA24₄
24-hr Activity Recall – ACT24₄
Subset Repeat DLW (n=50/site)
Subset Repeat RMR (n=50/site)
FFQ₂
Checklist₂
PA monitor₂
FR_{2A}
Fasting Blood₂
DEXA₂
PAQ₂

GROUP 3

Months 1-3

FFQ₁ Baseline
Checklist₁ Baseline
Anthropometry₁
2 UN_{1,2}
24-Hour Recall- ASA24₁
24-hr Activity Recall – ACT24₁
Subset Repeat DLW
Subset Repeat RMR
PA monitor₁
FR_{1A}
Fasting Blood₁
DEXA₁
PAQ₁

Months 4-6

Anthropometry₂
2 UN_{3,4}
24-Hour Recall- ASA24₂
24-hr Activity Recall – ACT24₂

Months 7-9

Anthropometry₃
2 UN_{5,6}
24-Hour Recall- ASA24₃
24-hr Activity Recall – ACT24₃
DLW
RMR
PA monitor₂ - at first DLW visit
Calibration PA monitor, if needed – at second DLW visit, with RMR
FR_{2B}
Fasting Blood₂
DEXA₂
PAQ₂

Months 10-12

Anthropometry₄
2 UN_{7,8}
24-Hour Recall- ASA24₄
24-hr Activity Recall – ACT24₄
FFQ₂
Checklist₂

GROUP 4

Months 1-3

FFQ₁ Baseline
Checklist₁ Baseline
Anthropometry₁
2 UN_{1,2}
24-Hour Recall- ASA24₁
24-hr Activity Recall – ACT24₁

Months 4-6

Anthropometry₂
2 UN_{3,4}
24-Hour Recall- ASA24₂
24-hr Activity Recall – ACT24₂
Subset Repeat DLW
Subset Repeat RMR
PA monitor₁
FR_{1B}
Fasting Blood₁
DEXA₁
PAQ₁

Months 7-9

Anthropometry₃
2 UN_{5,6}
24-Hour Recall- ASA24₃
24-hr Activity Recall – ACT24₃

Months 10-12

Anthropometry₄
2 UN_{7,8}
24-Hour Recall- ASA24₄
24-hr Activity Recall – ACT24₄
DLW
RMR
FFQ₂
Checklist₂
PA monitor₂- at first DLW visit
Calibration PA monitor, if needed - at second DLW visit, with RMR
FR2A
Fasting Blood₂
DEXA₂
PAQ₂