Optimizing Energy Balance Highlights of Progress

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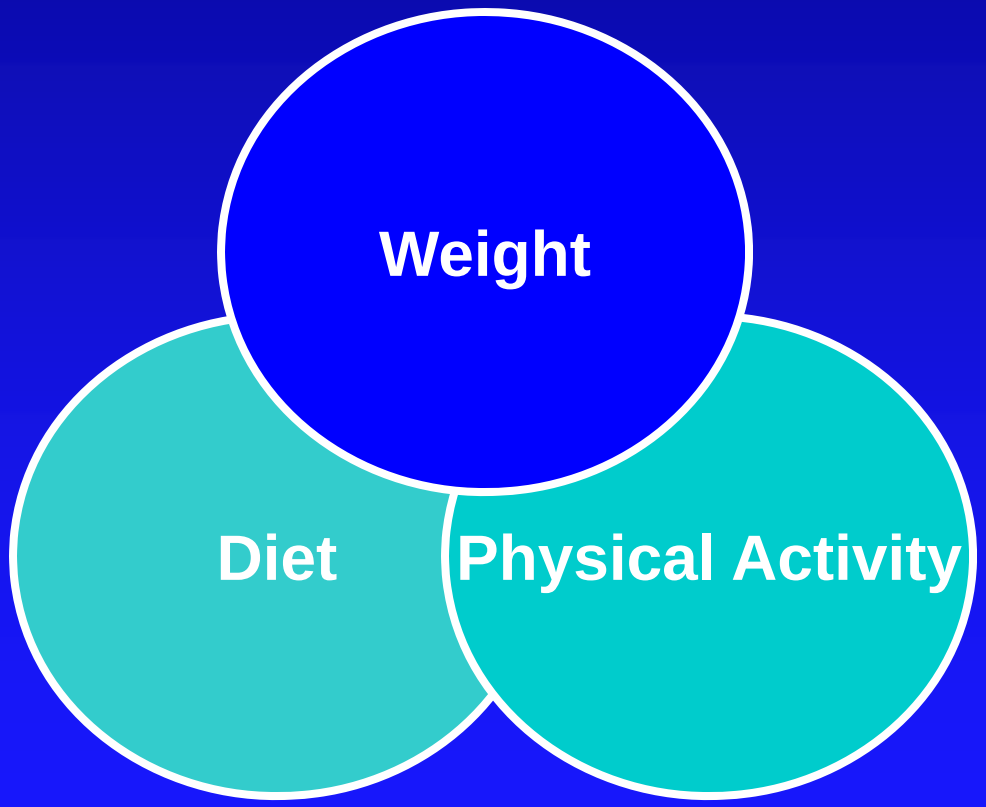
Energy Balance, Energetics and Cancer



NCI Energy Balance Initiative: Timeline

- **July 2002** - Director A. von Eschenbach calls for Energy Balance Initiative
- **2002/2003** - NCI Energy Balance Priority Working Group
- **Fall 2003** - Optimizing Energy Balance to Reduce the Cancer Burden included in 2005 Bypass Budget

Goals of the NCI Energy Balance Initiative

- Understand the causes of adverse patterns of weight, physical activity and diet
- Define their contribution to cancer
- Apply this knowledge to cancer prevention and control.

Specific Objectives of the Initiative

1. Discover how body weight, physical activity, and diet, along with genetic and environmental factors, interact over a lifetime to influence the cancer process
2. Monitor trends in and determinants of diet, weight, and physical activity and their cancer-related consequences by expanding nationwide research and surveillance infrastructure
3. Develop improved measurement methods of body mass and composition, physical activity and fitness, diet, and bioactive food components through self-report measures and advances in technology for objective reference measures
4. Improve cancer-related health outcomes, especially in high risk populations, by accelerating research on energy balance-related behaviors and developing interventions

Objective 1

- Discover and characterize mechanisms leading to cancer by initiating transdisciplinary research centers in the areas of energetics, physical activity, nutrition, and genetics. $6.00 M
- Collect enhanced self-report and objective measures on diet and bioactive food components, body mass and composition, and physical activity and fitness by expanding and using existing population-level studies, including the Cohort Consortium. $5.00 M
- Advance understanding of cancer mechanisms by conducting studies in existing NIH clinical metabolic and nutrition research units. $1.00 M
- Document the influence of energy balance on the cancer process throughout life through the use of preclinical animal models. $3.00 M
- Study the impact of energy balance on cancer by initiating basic and clinical research utilizing proteomic approaches and molecular technology. $3.00 M

Objective 2

- Expand nationwide surveys to enhance self-report, biologic, and genetic measures for monitoring and examining the impact of behaviors related to energy balance and cancer, in collaboration with the National Center for Health Statistics (NCHS). $2.00 M
- Advance knowledge about specific local populations by fostering community surveillance on individual behaviors and environmental factors, in collaboration with the Centers for Disease Control and Prevention and NCHS. $3.00 M
- Develop an infrastructure to train future national and international scientific leaders on the importance of energy balance across the cancer continuum by supporting interdisciplinary training in both basic and population sciences. $2.50 M
- Evaluate public comprehension of health recommendations on physical activity and nutrition through the NCI Health Information National Trends Survey (HINTS). $0.50 M
- Establish surveys of healthcare providers to evaluate knowledge, attitudes, and practice related to weight control in clinical practice. $1.00 M
- Identify opportunities for cancer control by developing a research resource on legislative policies related to nutrition, physical activity, and obesity. $1.00 M
- Initiate innovative research on economic factors related to diet, physical activity, and energy balance in at-risk populations, in collaboration with Federal partners, including the U.S. Department of Agriculture. $2.50 M

Objective 3

- Expand validation research of diet, physical activity, and fitness measurement through the use of reference biomarkers and physical measures of fitness within national and international cohort studies. $5.00 M
- Support research in collaboration with other NIH institutes in innovative technologies, such as electronic handheld monitoring devices and Internet surveys, in the assessment of diet, weight control, and physical activity behaviors. $2.00 M
- Improve the ability to capture information on diet, weight, and physical activity behaviors across diverse cultural populations. $5.00 M
- Develop surrogate (intermediate) biomarkers for use as predictors of the effectiveness of diet and physical activity interventions. $1.50 M

Objective 4

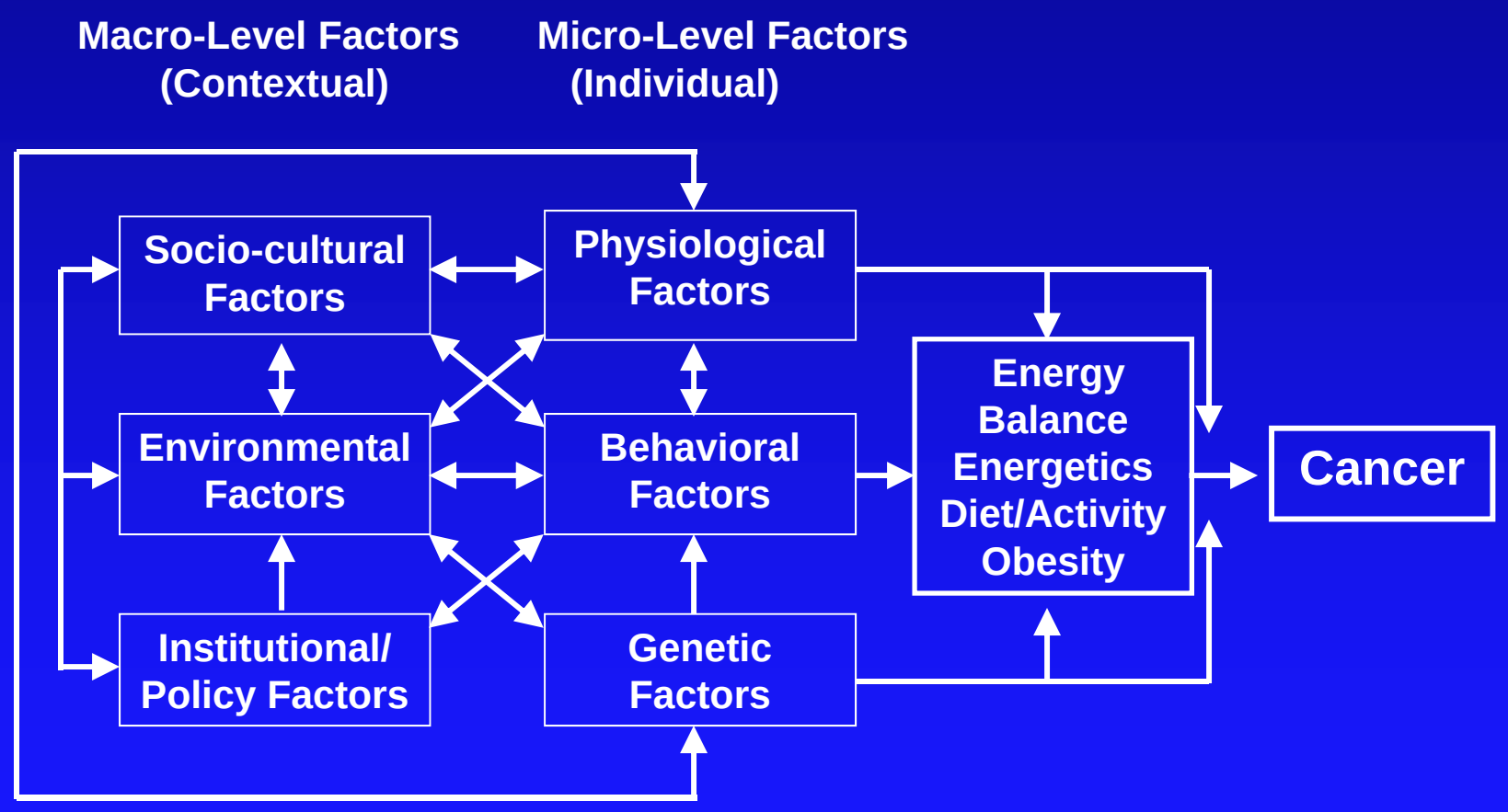
- Support research on interventions that focus on weight control through diet and physical activity in cancer patients and in populations at high risk for cancer. $4.00 M
- Support research to understand how sociocultural factors influence adoption of recommended behaviors, and develop approaches to improve interventions in specific populations. $3.00 M
- Develop effective approaches to improving and targeting health messages in the areas of dietary guidance, physical activity recommendations, and food labeling by supporting health communication research in partnership with other NIH institutes. $2.00 M
- Support research within transdisciplinary research centers on innovative and cost-effective obesity prevention interventions, with broad population impact at the social-environmental or policy level for children and adults. The research on efforts targeting adults should focus on critical periods when weight gain is likely to occur, such as with smoking cessation, pregnancy, stress, depression, injury, or cancer treatment. $4.00 M

Objective 1:

Discover how body weight, physical activity, diet, along with genetic and environmental factors, interact over a lifetime to influence cancer process

- TREC RFA
- Basic Research on Energy Balance and Cancer: Animal Models
- NIH Clinical Center Interventions
- NCI Funded Epidemiologic Studies Explore Energy Balance & Cancer Risk
- Analyses of Energy Balance related Biomarkers in Population Studies

TREC Conceptual Model



Barriers to Progress

- Research is limited on the intersection of diet, weight and physical activity
- Most research is not transdisciplinary
- Need to engage research disciplines not previously playing a large role in biomedical research
  - Urban planning, transportation, communications
- Need to bridge multiple disciplines to identify individual and population level solutions to a complex health problem

Two Major Challenges

- Enhancing understanding of the mechanisms underlying the association between energy balance and carcinogenesis across the cancer continuum and the life cycle

- Developing effective approaches with broad population impact at the social-environmental and policy level for the prevention and control of obesity
  - Focusing on children and adults during critical periods for excessive weight gain

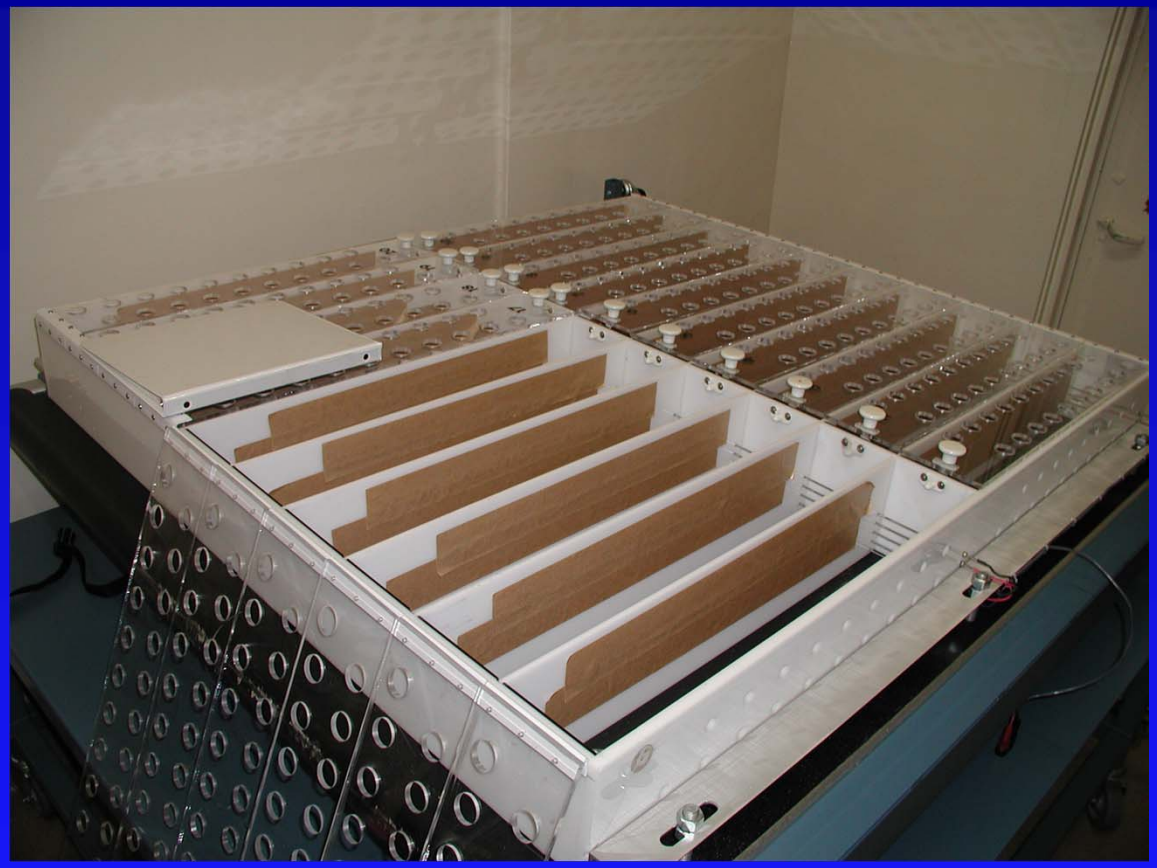
What is “Transdisciplinary?”

- Development and application of a shared, integrative conceptual framework based on discipline-specific theories, concepts, and methods
- Instead of working in parallel, investigators collaborate across levels of analysis and intervention to develop a comprehensive understanding of energy balance and cancer

Energy Balance in Carcinogenesis: Rodent Models

- NCI intramural research by Drs. Hursting, Barrett and others has focused on the IGF pathway and on the role of calorie restriction in cancer prevention and control
- Examining the interactive effects of physical activity and diet on body composition, gene expression, and carcinogenesis in mouse models of breast and colon cancer

Treadmill Exercise and Polyp Formation in APC Min Mice

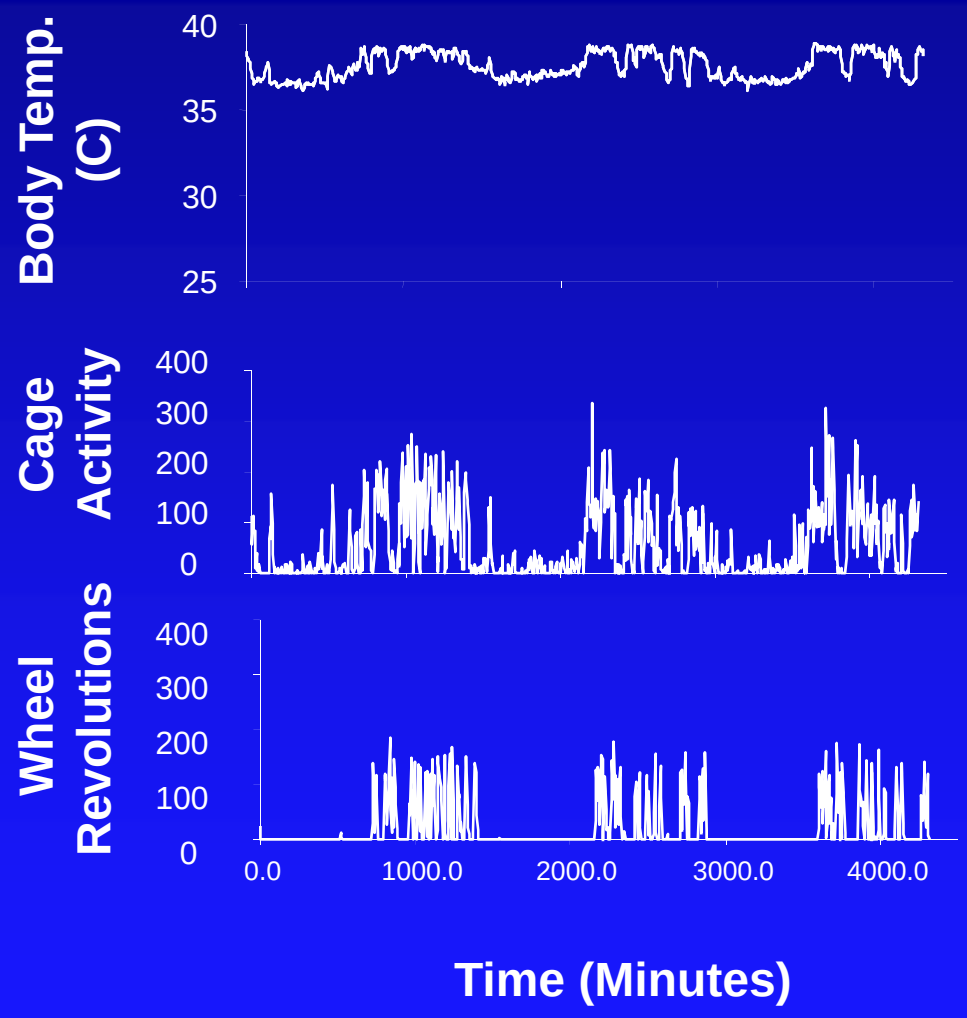


Colbert et al Med Sci Sports Exerc. 2003 Oct; 35(10): 1662-9.

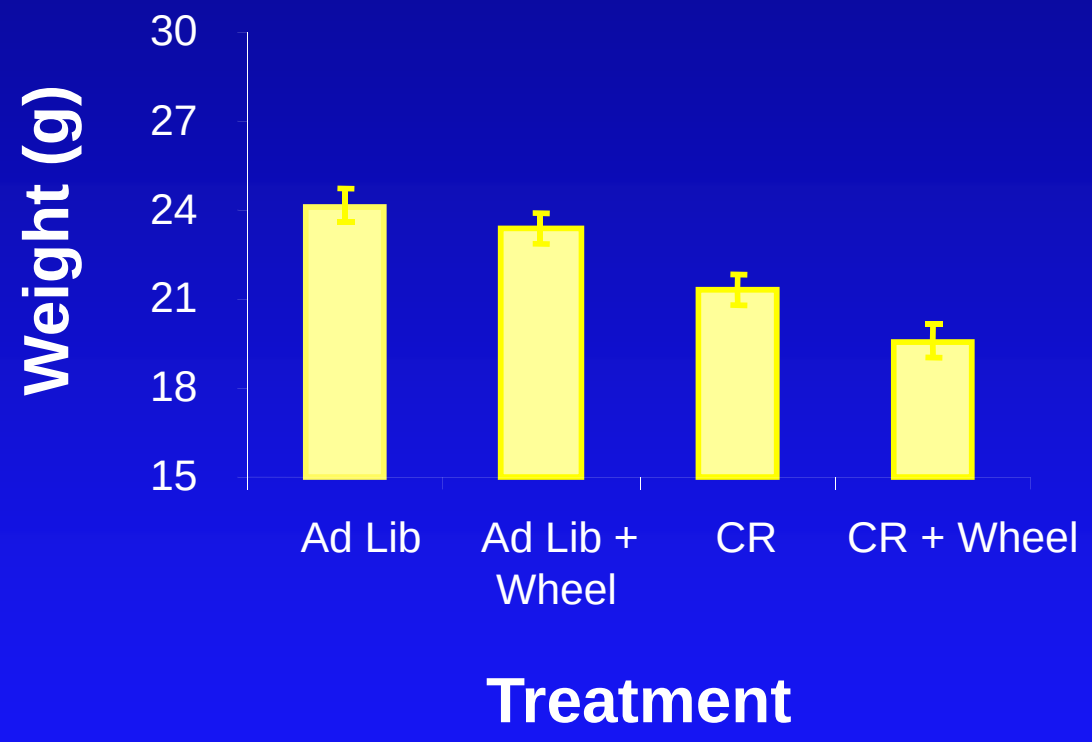
Current Studies: Exercise, Diet, Gene Expression, and Carcinogenesis in C57BL/6 and MMTV WNT-1 Mice

Colbert et al. In Prep; Berrigan et al. Prep

Measurement of Routine and Running Wheel Physical Activity and Body Temp. in C57BL/6 Mice



Combined Effects of Diet and Exercise on Mouse Weight



Conclusions: Animal models for Physical Activity and Carcinogenesis

- Much past research on energy balance and cancer in animal models has focused on calorie restriction
- New research is aimed at effects of physical activity and its interaction with diet
- These studies should help understand the biological basis of epidemiological associations between Physical Activity and Cancer

Wild Type / A-ZIP/F-1

Fat specific expression of a dominant negative that inhibits C/EBP and JUN B-ZIP families abolishes fat tissue: the only reported "fatless" mouse.

Jaideep Moitra

Physical Activity Intervention NIH Clinical Center

- Pilot Feasibility: 10,000 steps
- Phase II studies
  - Obese
  - Primary breast prevention
  - Secondary breast prevention
- Molecular studies
  - Hormonal
  - Immune
  - HIF

JoAnne Zujewski

NCI Extramural Epidemiologic Studies Explore Energy Balance & Cancer Risk

- **Breast Cancer**
  - Tamoxifen reduced the risk of breast cancer recurrence & mortality in women w/ ER+ tumors, regardless of BMI status
  - Obesity associated with an increased risk of recurrence of contralateral breast cancer
  - Reduced breast cancer risk observed in women w/ highest vs. lowest tertile of average lifetime physical activity
- **Rectal Cancer**
  - Participation in vigorous activity over the past 20 yrs. conferred the greatest protection against rectal cancer for both men & women

Objective 2:

Monitor trends in and determinants of diet, weight, and physical activity and their cancer-related consequences by expanding nationwide research and surveillance infrastructure

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- Enhanced Surveillance of Energy Balance Related Health Behaviors:
  - National Health Interview Survey (NHIS)
  - California Health Interview Survey (CHIS)
- Physical Activity and the Built Environment
- Objective Measurement of Physical Activity:
  - National Health and Nutrition Examination Survey (NHANES)

Enhanced Surveillance of Energy Balance Related Health Behaviors: The National and California Health Interview Surveys

- Validation of Screeners i.e. fruits and vegetables
- Expanded assessment of physical activity in multiple domains, particularly walking for both leisure and non-leisure time activities
- Detailed studies of associations between energy balance related behaviors and level of acculturation in Hispanic populations
- Planning for the incorporation of novel data elements characterizing neighborhood environments in the California Health Interview Survey
- Participating in planning of trans NIH Obesity Research Task Force initiative on Built Environment – led by NIEHS

Energy Balance and the Built Environment

- Built environment or neighborhood factors have tremendous potential to influence physical activity and diet
- RFA and conference “Obesity and the Built Environment: Improving Public Health through Community Design” – NIEHS led
- Ongoing efforts:
  - Analyses of environmental effects in existing surveys
  - Incorporation of novel measures of the built environment into the California Health Interview Survey
  - Expanded questions concerning walking and neighborhood characteristics in CHIS and NHIS
  - Inclusion of specific language in the TREC RFA calling for research on contextual effects on health behaviors

Association between Walking Frequency and Home Age

Walking Freq.	When Residence Built				
	< 1946		1946-1973		≥ 1974
	Crude	Adjusted	Crude	Adjusted	(Reference)
≥ 20/Month	**1.48**	**1.53**	**1.45**	**1.47**	1.00
	(1.01-2.19)	(1.08-2.15)	(1.15-1.83)	(1.18-1.84)	
0 - 20/Month	1.06	1.14	1.01	1.17	1.00
	(0.83-1.36)	(0.89-1.45)	(0.81-1.28)	(0.87-1.57)	
0/Month	1.00	1.00	1.00	1.00	

Berrigan and Troiano, Am J Prev Med 2002

Objective Measurement of Physical Activity in NHANES

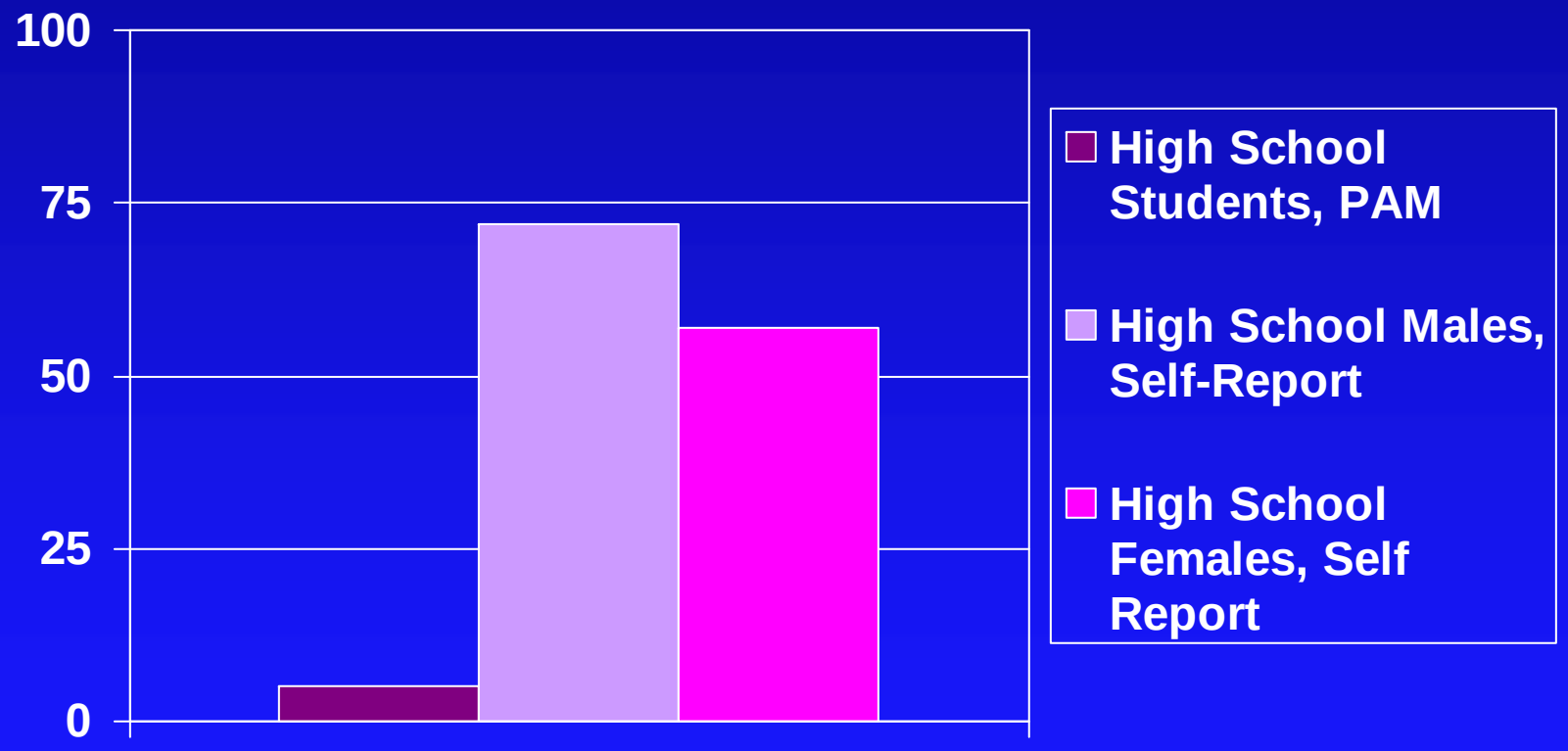
- Ages 6 years and over
- Ask for 7 d of use while awake
- Mail back monitor
- Recruitment rate 93%
- Monitor return rate 96%
- 10+ hr/day use for 4-7 days by ~75% of participants

Activity Monitor

Why Use Activity Monitors?

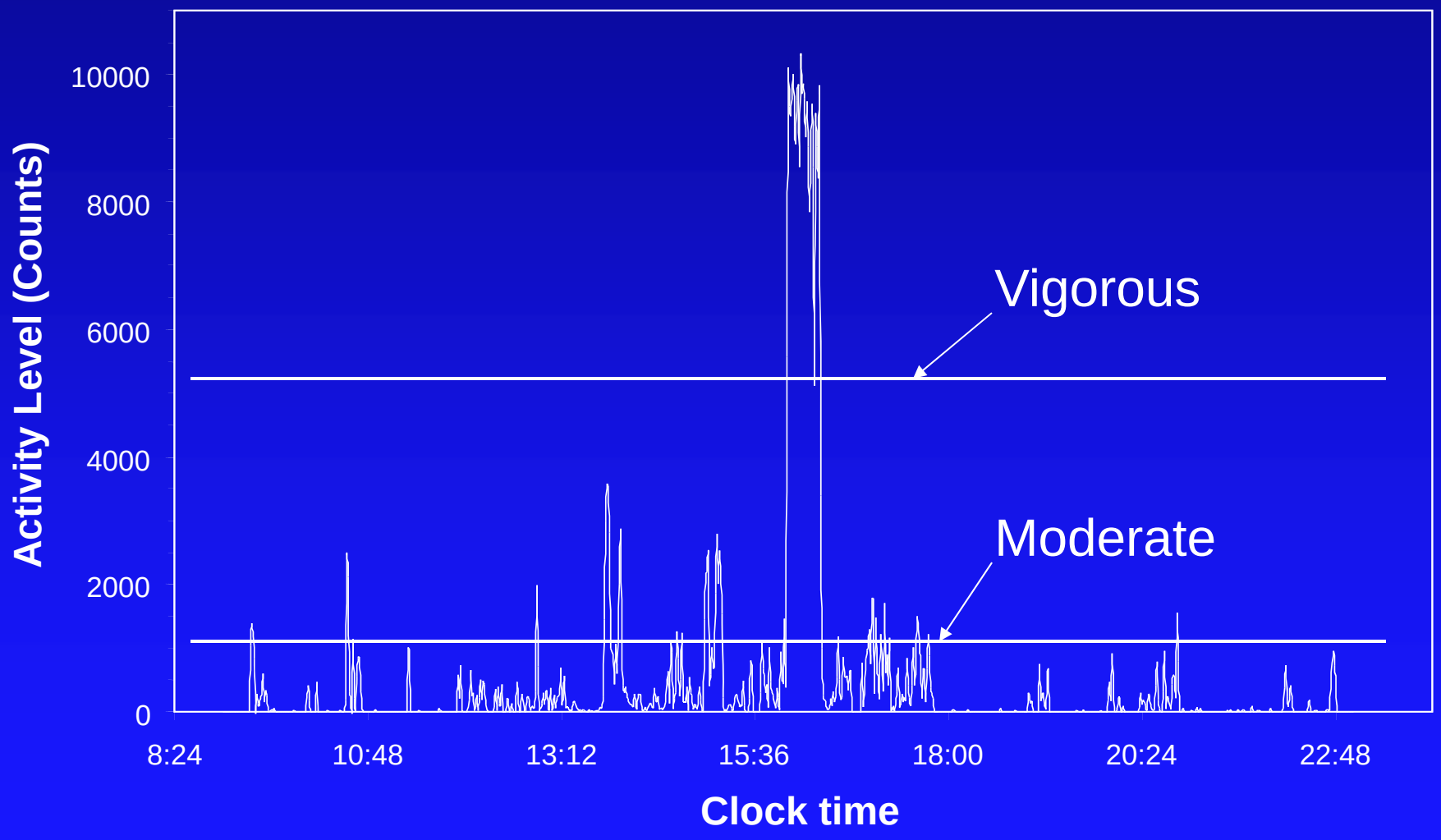
- Desire data for children
  - They lack cognitive skills to report frequency & duration
  - Proxies do not observe them for much of day
- Reduce error due to misreports for adolescents and adults
  - Especially hard to report “routine” activity
- Monitors advantages:
  - Remove cognitive reporting aspect
  - Capture steps and intensity

Percent of Teens Meeting Health Objective: PAM vs. Self-Report



Pate et al, 2002

Example: Human Activity Counts



Objective 3:

Improve measurement methods of body mass and composition, physical activity and fitness, diet, and bioactive food components through self-report measures and advances in technology for objective reference measures

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- Observing Protein and Energy Nutrition (OPEN) Study and Follow-up (Open II)
- Improving Diet and Physical Activity Assessment (PAR-03-009)
  - **NCI led trans NIH initiative**
- Capturing Physical Activity and Diet in Real Time
- Bioengineering Approaches for Prevention and Treatment of Overweight and Obesity
  - **NHLBI led trans NIH initiative**

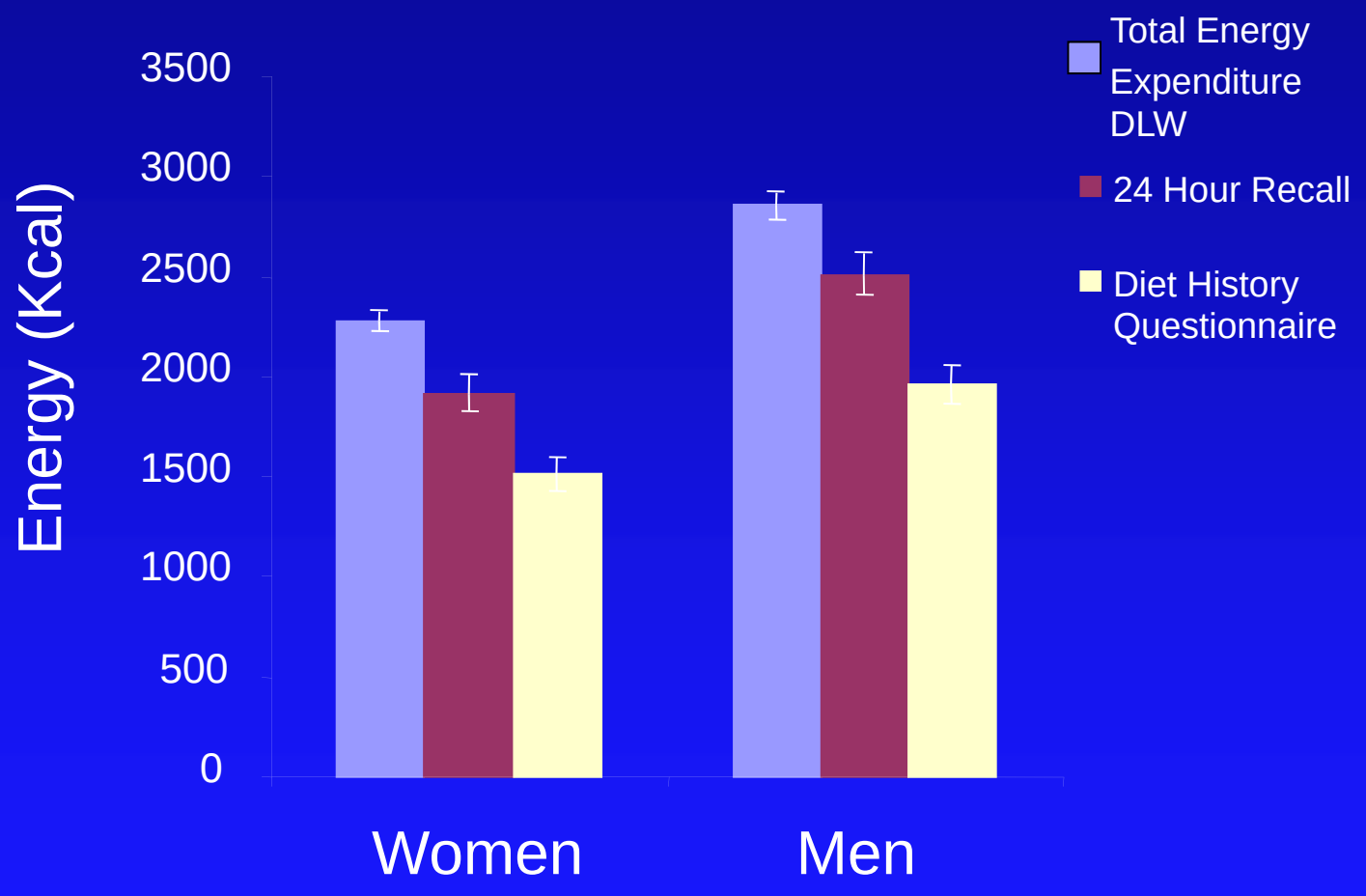
Improving Diet and Physical Activity Assessment (PAR-03-009)

- Objective: Support research to improve diet and physical activity measurement through improved instruments, technologies, or statistical/analytic techniques.
- Co-sponsors: NIA, NIDDK, NINR
- Progress: 34 applications received, 20 reviewed, 14 scheduled for review, and 3 awaiting approval for funding.

Observing Protein and Energy Nutrition (OPEN) Study: Epidemiologic Results

- Estimated association between diet and cancer is more affected by measurement error than previously thought
  - A true doubling of risk could be estimated as an increase of only 10% (i.e., RR of 2.0 appears to be 1.1)
- Diet studies may be severely compromised *a priori* because of this measurement error
- Could account for null results from epidemiologic studies

Energy Intake Underestimated by Self-Report in Men and Women



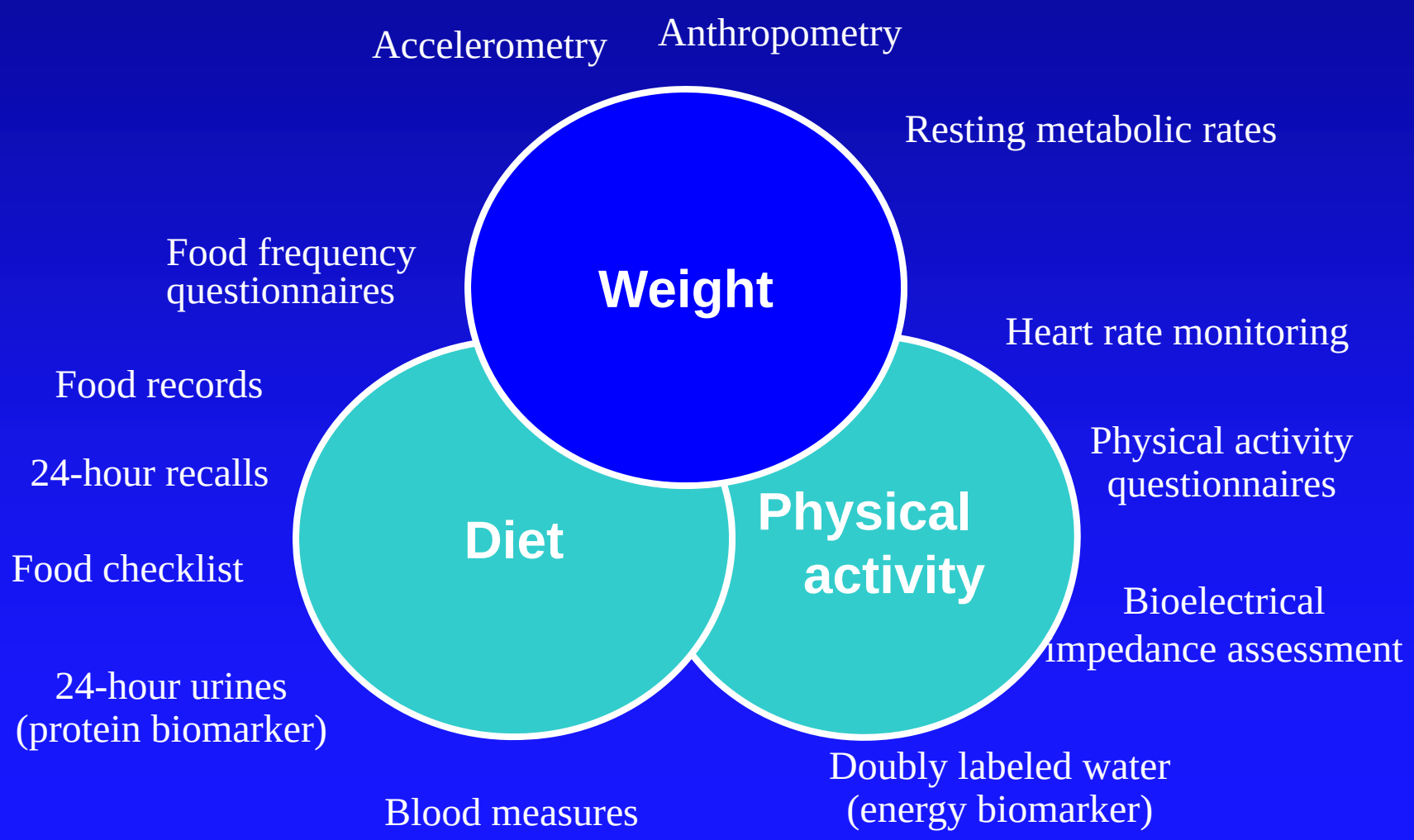
Dietary Measurement Error and Implications of the OPEN Study

- Need for replication of the findings in diverse populations and incorporation of additional assessment instruments.
- Expand from dietary measurement error to concentrate on both sides of the energy balance equation: physical activity as well as dietary intake.
- Transdivisional working group (DCCPS, DCP, DCEG) has designed a new study (OPEN II) to advance understanding of measurement error in both diet and physical activity.

OPEN II Planning

- Conduct a new biomarker study in existing cohorts to explore measurement error and necessary adjustment of risk estimates in heterogeneous populations
- Emphasize energy balance: inclusion of multiple measures of physical activity
- Include additional dietary assessment measures (e.g., dietary records)
- Investigate novel methods to decrease the effect of measurement error

OPEN II: Data to be collected



Capturing Physical Activity and Diet in Real Time

- Working Group Meeting in January 2004
- Nationally recognized experts in physical activity and nutrition research
- Discussed opportunities and challenges of using real-time methodologies and associated e-technologies to assess and modify physical activity, diet, and obesity/energy balance

Objective 4:

Improve cancer-related health outcomes, especially in high risk populations, by accelerating research on energy balance-related behaviors and developing interventions

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- Transdisciplinary Research on Energetics and Cancer (TREC)
- Policy research
- Other extramural funding efforts

Policy Related Research: Developing Research Resources

- Tracking Physical Activity and Nutrition-Related Legislative Policies and their Impact
  - Pilot effort initiated on including data in a research resource
  - Coordination with other efforts
- Understanding Public Health Recommendations in Physical Activity and Nutrition: Health Promotion Model in the HINTS Survey
  - Added questions to the HINTS 2003 survey

Office of Cancer Survivorship: Ongoing Extramural Research

- Examine the feasibility and benefits of a home-based moderate exercise program among breast cancer survivors
- Measure the effects of exercise or exercise plus diet intervention on preventing weight gain and adverse changes in body composition, reducing depression, improving quality of life and influencing biomarkers associated with breast cancer and other co-morbid conditions
- Establish feasibility and generate initial outcome data concerning the phvsical and psvcholoqical health benefits of a group exercise training program for women with recently diagnosed metastatic breast cancer.

NCI Synthesis and Dissemination

- Support of evidence based reviews
- Update of NCI fact sheets
  - Obesity
  - Physical activity
- Highlights in NCI Director's Bulletin
- NCI/OD activities
  - To be described by Dr. Maibach

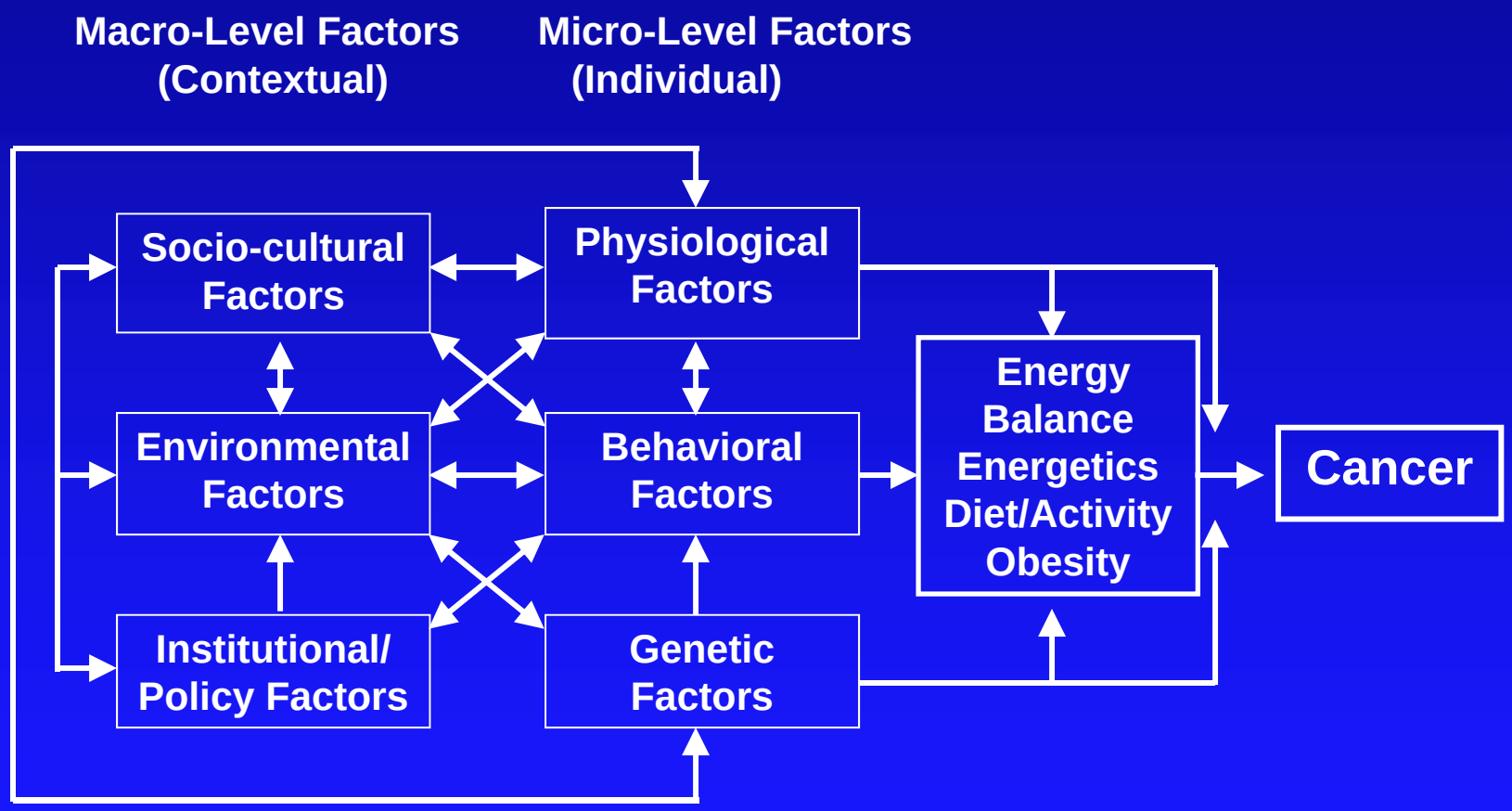
NIH Obesity Research Task Force

- Cross NIH
- Obesity Research Strategic Plan
  - Draft released on NIH web Feb 12th
  - Comment period Feb 12-26
- Addresses basic to population sciences
- Stimulating trans NIH initiatives
- Active NCI participation

NIH Obesity Research Outcome Goals

- Evaluate the effectiveness and assure translation of strategies to maintain healthy weight in children and adults through behavior (activity, diet) change which can be applied in a home, school, or workplace environment

- Use knowledge of regulation of energy storage and food intake to develop new therapeutic modalities (including drugs, surgery, and other technologies) to complement lifestyle interventions

- Use knowledge of mechanisms whereby obesity increases risk for co-morbidities to develop potential therapeutic approaches for ameliorating these conditions independent of weight loss

The Challenge – The Opportunity