Mathematical Modelling Weight Gain and Weight Loss in Children and Adolescents

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Energy Cost of Weight Gain

- Conventionally, energy cost of growth has not been based on a dynamic mathematical model
  - ECG = Energy deposition + Energy cost of synthesis

- Energy deposition depends on the accurate assessment of body composition

  Chemical maturation and differential contribution of various organs to weight gain influence ECG

  Proportion of protein to fat tissue varies with age, gender and maturation

- Energy cost of synthesis depends on the efficiency of conversion of dietary substrates into tissue constituents

Energy Cost of Growth

- Theoretical approach based on stoichiometry of biochemical reactions
  - Chemical composition of organs and tissues to calculate increases in protein, TG, phospholipids, cholesterol, glycogen, DNA, RNA (Hommes 1975)
    - Energy cost of synthesis 0.3 kcal/g gained
    - Energy deposition (14% P, 10% F) 1.6 kcal/g gained
    - Total ECG 1.9 kcal/g gained
  - 100% energetic efficiency (metabolic interconversions, futile cycling, ion leakage, etc.)
- Empirical data from balance studies in fast-growing infants/children
  - Slope of metabolizable energy intake (MEI) regressed on weight gain
  - Difference between MEI and EE/weight gain
  - Sum of energy deposition and energy synthesis
- Empirical data based on body composition studies
  - Energy deposition estimated from energetic equivalents for protein and fat accretion

Modelling Weight Gain

- Christiansen et al. (2005) published a dynamic mathematical model of weight gain in adults which integrated the increasing energy required to maintain the body and sustain weight gain.
- Butte NF, Christiansen E and Sørensen TIA (2007) developed mathematical model based on empirical data and human energetics to predict the total energy cost of weight gain and obligatory increase in energy intake and/or decrease in physical activity level associated with weight gain in children and adolescents.
  - energy partitioning into fat and lean tissue during growth
  - energetic efficiency of tissue synthesis
  - higher basal energy expenditure in children.

Obesity, 2007;15:3056-3066

VIVA LA FAMILIA STUDY: Baseline Anthropometry

	Boys		Girls	
	Nonobese	Obese	Nonobese	Obese
N	228	281	276	240
Age (y)	11 ± 4*	11 ± 4	10 ± 5	11 ± 4
Weight (kg) †	43 ± 20[a]	71 ± 30[b]	38 ± 18[a]	64 ± 25[c]
Height (cm) ‡	143 ± 23	148 ± 19	134 ± 21	143 ± 17
BMI (kg/m^2) †	20 ± 4[a]	31 ± 7[b]	20 ± 4[a]	30 ± 6[b]
BMI (Z-score) §	0.7 ± 0.7	2.4 ± 0.4	0.6 ± 0.8	2.2 ± 0.3

*Mean±SD

†Age (P=0.001), Gender x BMI status (P=0.03)

‡ Age, Gender, BMI status (P=0.001)

§ Gender, BMI status (P=0.002)

Butte NF Am J Clin Nutr 2006;84:646-54

Anthropometric Changes

	Boys		Girls	
	Nonobese	Obese	Nonobese	Obese
N	228	281	276	240
Weight gain (kg/y) †	4.7 ± 2.5 *	8.2 ± 3.8	4.1 ± 2.4	6.7 ± 3.5
Height (cm/y) ‡	5.4 ± 2.4	5.5 ± 2.2	4.6 ± 2.8	4.7 ± 2.6
BMI (units/y)	0.9 ± 1.1	1.7 ± 1.5	1.1 ± 1.1	1.7 ± 1.6
BMI z (SD/y) §	0.10 ± 0.36	-0.01 ± 0.18	0.14 ± 0.38	- 0.001 ± 0.14

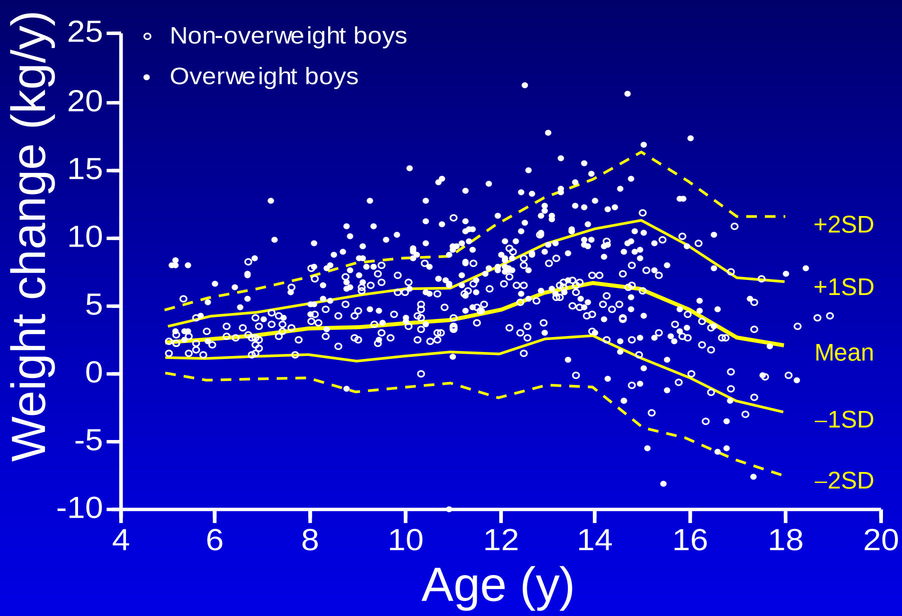
*Mean ± SD

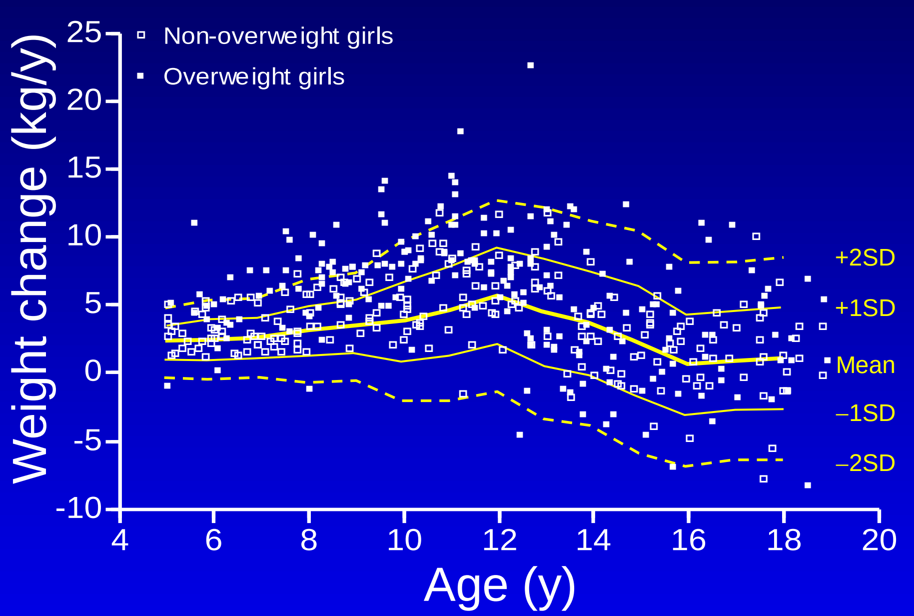
† Adjusted for age, age^2 and Tanner stage, sex and BMI status ($P<0.05$)

‡ Adjusted for age, age^2 and Tanner stage, sex ($P=0.001$)

§ Adjusted for age, age^2 and Tanner stage, BMI status ($P=0.001$)

1-y Changes in Weight Relative to Fels Reference





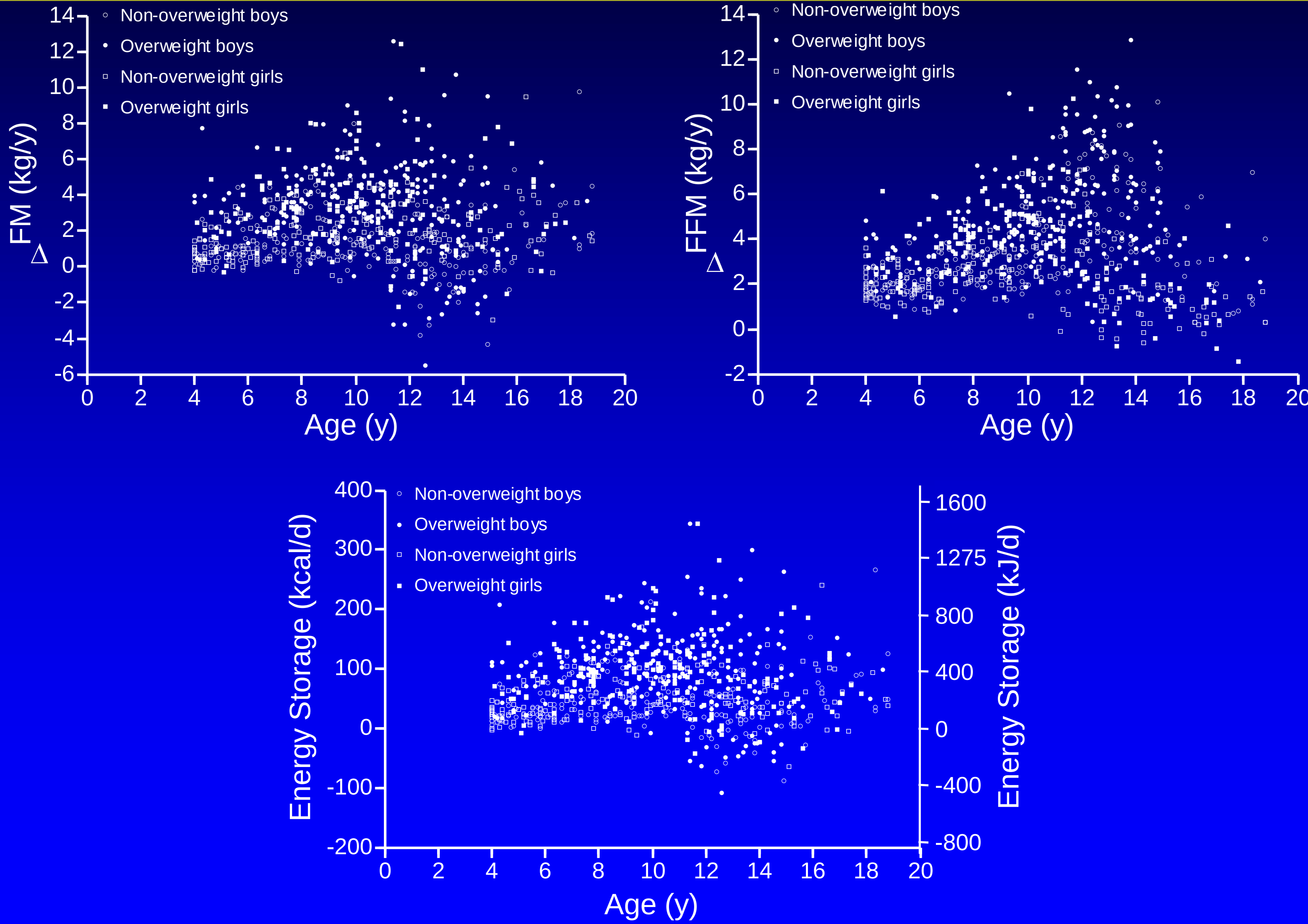
Changes in Body Composition by DXA

	Boys		Girls	
	Nonobese	Obese	Nonobese	Obese
N	228	281	276	240
FFM (kg/y) †	3.5 ± 2.0	5.1 ± 2.3	2.2 ± 1.4	3.6 ± 2.0
FM (kg/y) †	1.2 ± 1.8	3.1 ± 2.7	1.7 ± 1.5	3.2 ± 2.3
%FM (%/y)	0.7 ± 3.5	0.3 ± 3.1	1.8 ± 3.0	1.0 ± 2.7

*Mean±SD

† Adjusted for age, age^2 and Tanner stage, sex and BMI status ($P<0.05$)

Energy Storage



Specification of the Model

- *BM* can be partitioned into *FM* and *FFM*, determined by the data for each child.
- *FM* and *FFM* each has a specific energy content, *cf* and *cff*, and a specific basal energy expenditure, *kf* and *kff*.
- The conversion of surplus energy intake into *FM* and *FFM* requires specific amounts of energy, given by the efficiencies *ef* and *eff* which are independent of energy imbalance and composition of food intake.
- Total energy expenditure = CE + DIEE + PAL · BMR
- The fraction of fat added in new tissue (*fr*) is independent of *BM* or weight gain.
- The fraction of fat added in new tissue (*fr*) is determined as the median for each gender-Tanner stage group.
- *BM* increases at a constant rate during the period.

Value of Constants

kf, kff: tissue-specific basal energy expenditure

- EE per kg FM = 6.45 kcal•kg^{-1}•d^{-1}
- EE per kg FFM =

boys: 44.6, 37.9, 33.8, 30.8, 28.9 kcal•kg^{-1}•d^{-1} (Tanner 1-5)

girls: 48.2, 40.2, 34.7, 31.4, 31.0 kcal•kg^{-1}•d^{-1} (Tanner 1-5)

cf, cff: energy storage

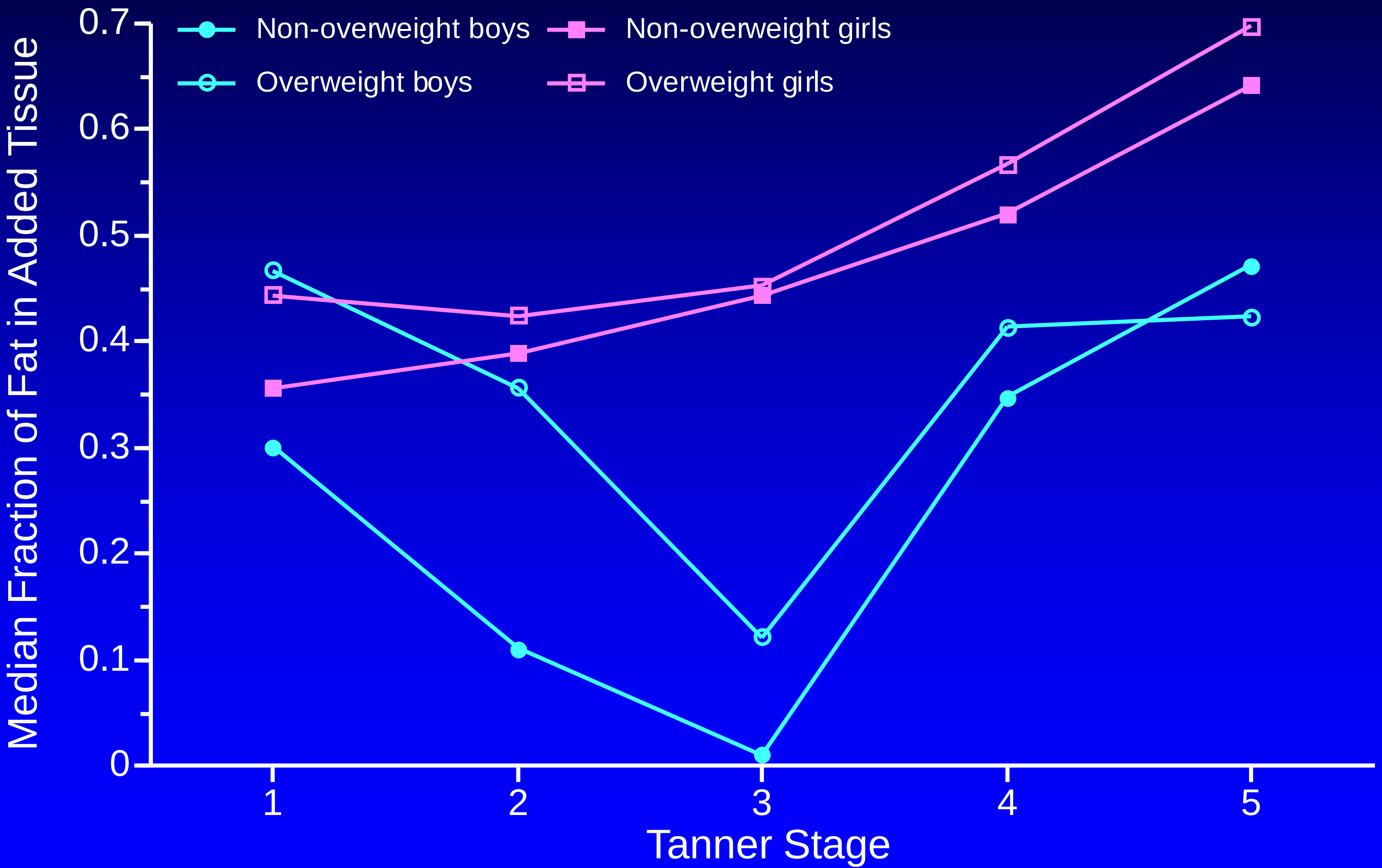
- EE per kg FM = 9.25 kcal/g
- EE per kg FFM = 1.07 kcal/g

ef, eff: efficiency energy conversion

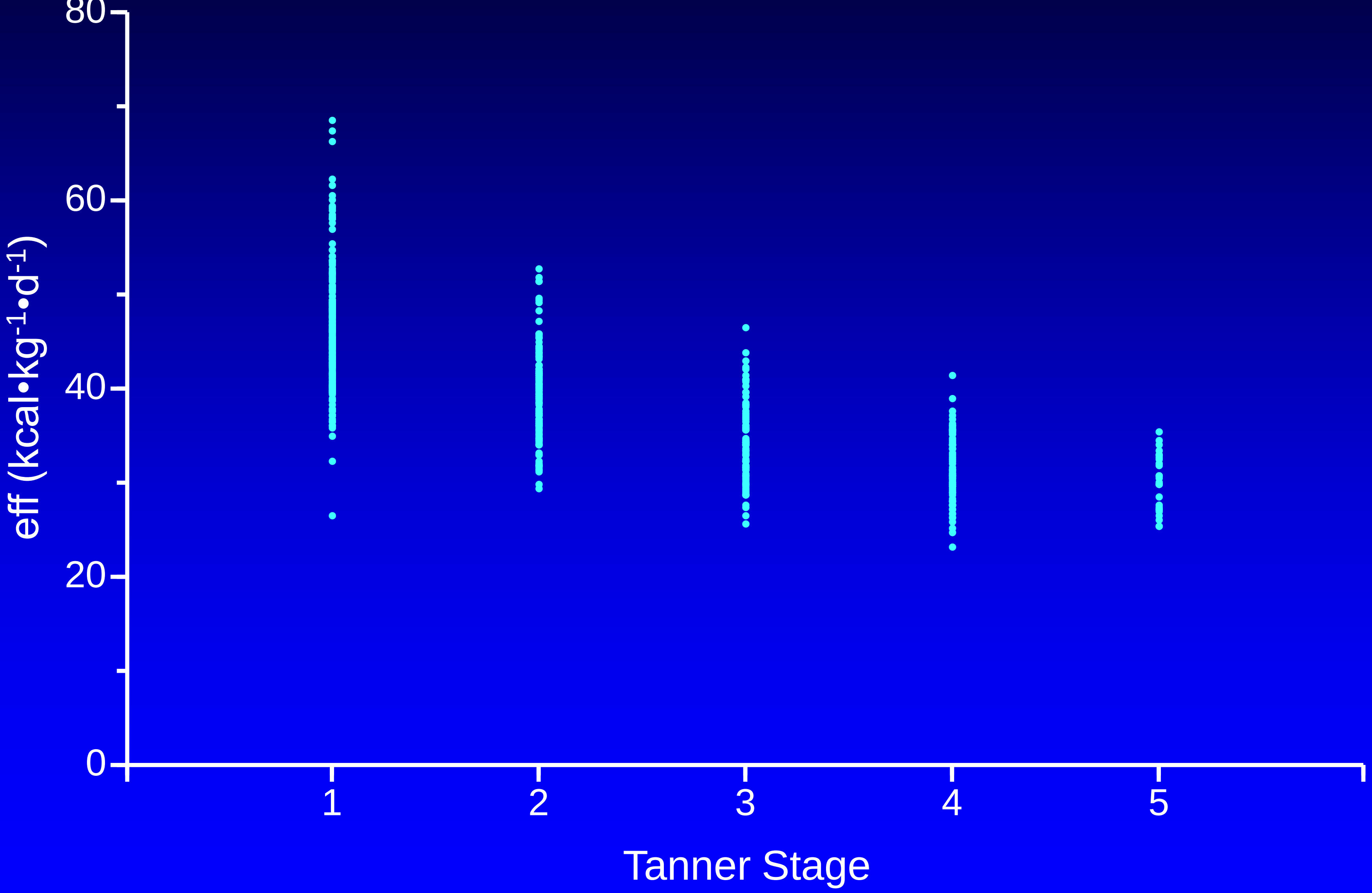
- Fat = 0.85
- Protein = 0.42

$$K_{coef} = k_f f_r + k_{ff} (1 - f_r)$$
$$C_{coef} = c_f f_r + c_{ff} (1 - f_r)$$
$$E_{coef} = c_f f_r / e_f + c_{ff} (1 - f_r) / e_{ff}$$

Measured Fraction of FM in Added Tissue

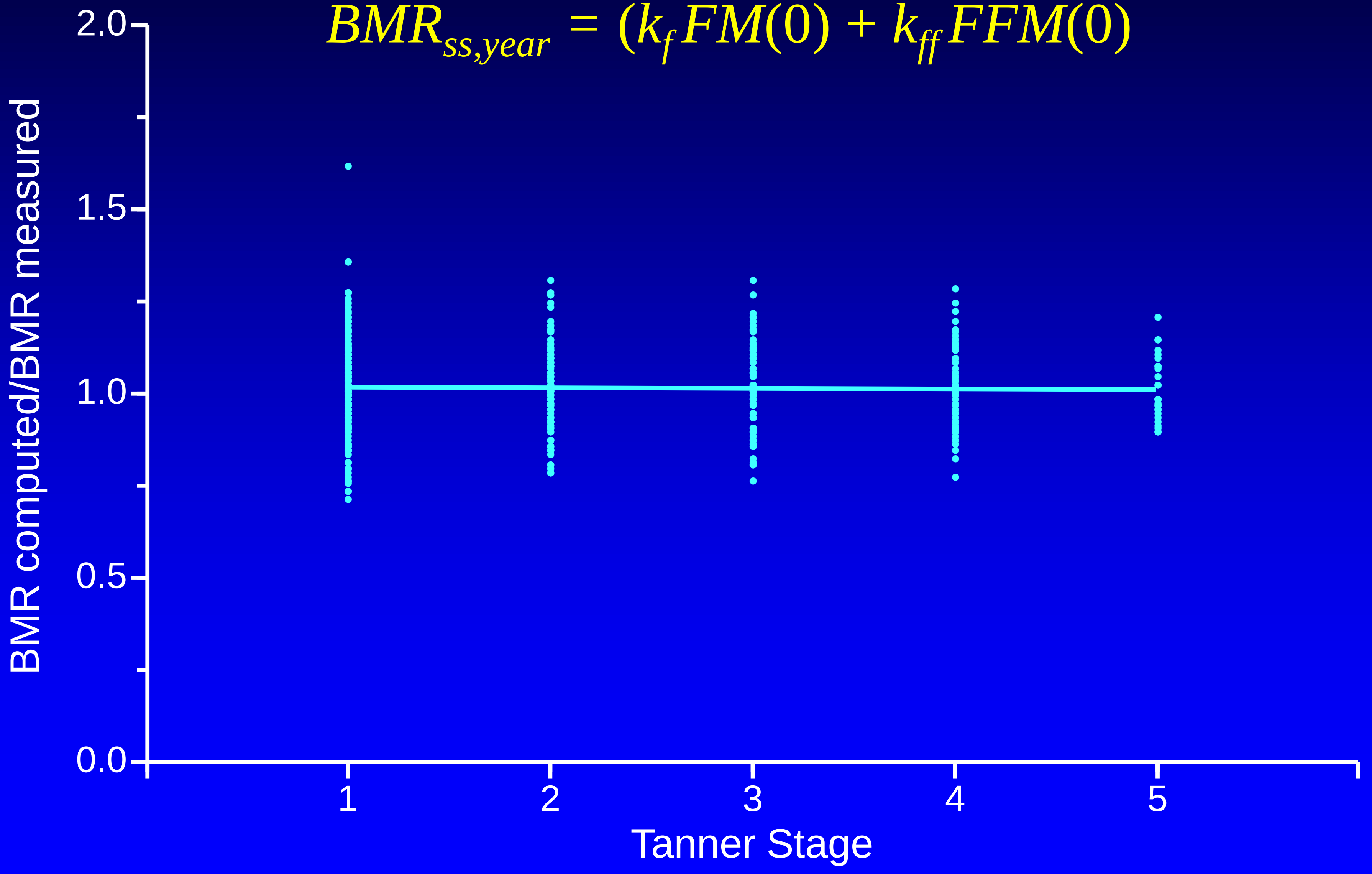


Measured Basal Energy Expenditure of FFM



Basal Metabolic Rate

$$BMR_{ss,year} = (k_f FM(0) + k_{ff} FFM(0))$$



Energy Cost of Weight Gain

1. Energy stored in added tissue (C)

$$\Delta C = (c_f f_r + c_{ff}(1 - f_r))\ \Delta BM = C_{coef}\,\Delta BM$$

2. Conversion energy (CE)

$$CE = (c_f f_r / e_f + c_{ff}\,(1 - f_r)/e_{ff})\ \Delta BM - \Delta C$$

3. EEss + EE added tissue

$$\begin{aligned} EE_{year} &= \int_0^{1y} PAL \cdot BMR(t)\, dt \\ &= PAL \int_0^{1y} (k_f FM(t) + k_{ff} FFM\,(t))\, dt \\ &= EE_{ss} + PAL \int_0^{1y} (k_f f_r + k_{ff}\,(1 - f_r))\ \Delta BM\ t\, dt \\ &= EE_{ss} + {}^{1}/_{2}\, 365\ PAL\ K_{coef}\ \Delta BM \end{aligned}$$

Energy Cost of Growth and Energy Intake

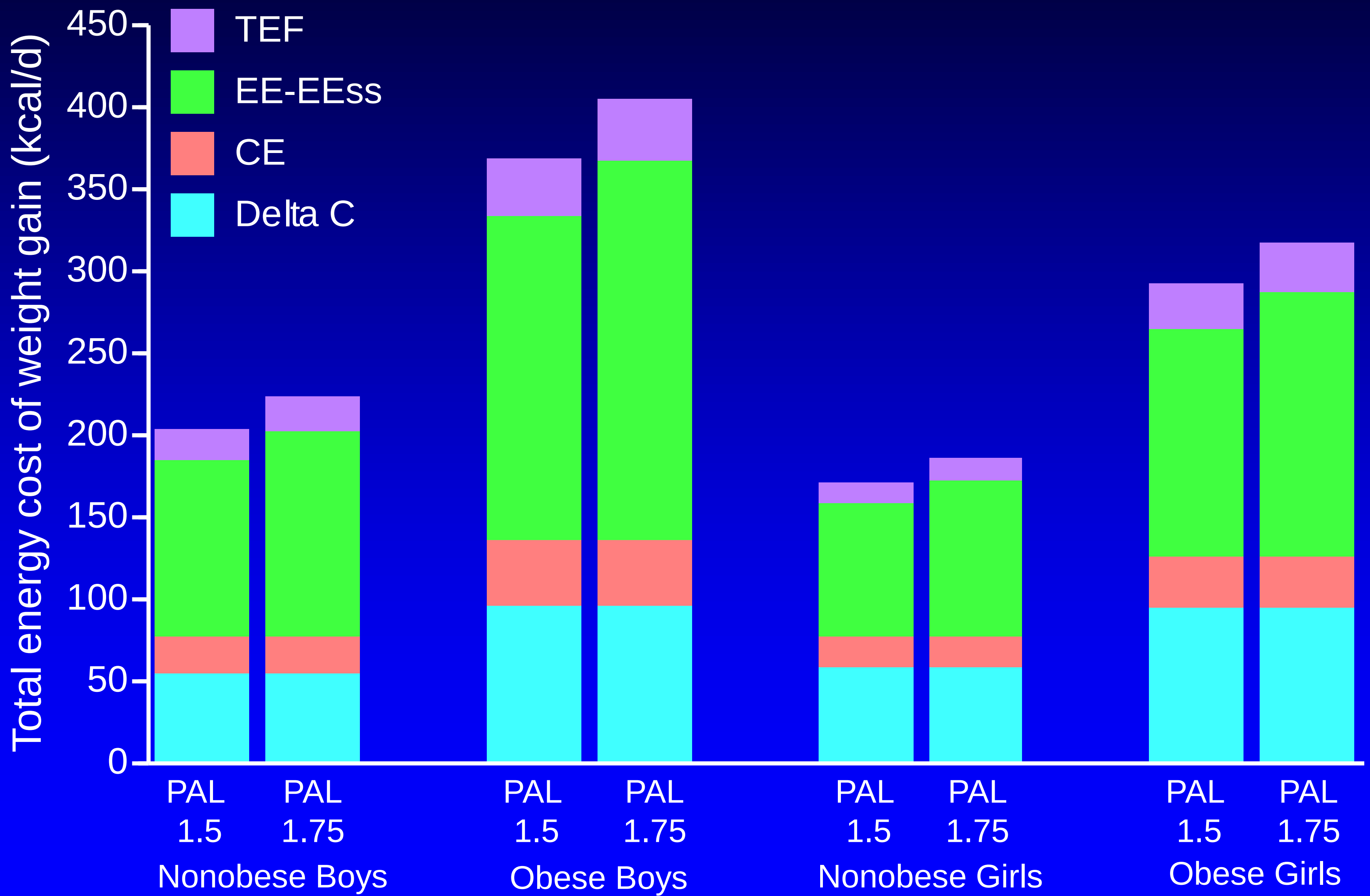
1. Energy cost of growth in 1 year:

$$ECG_{cost,year} = (\Delta C + CE + EE_{year} - EE_{ss,year}) / 0.9$$
$$= Ecoef + {}^{1}/_{2}\, 365\ PAL\ K_{coef}\ \Delta BM / 0.9$$

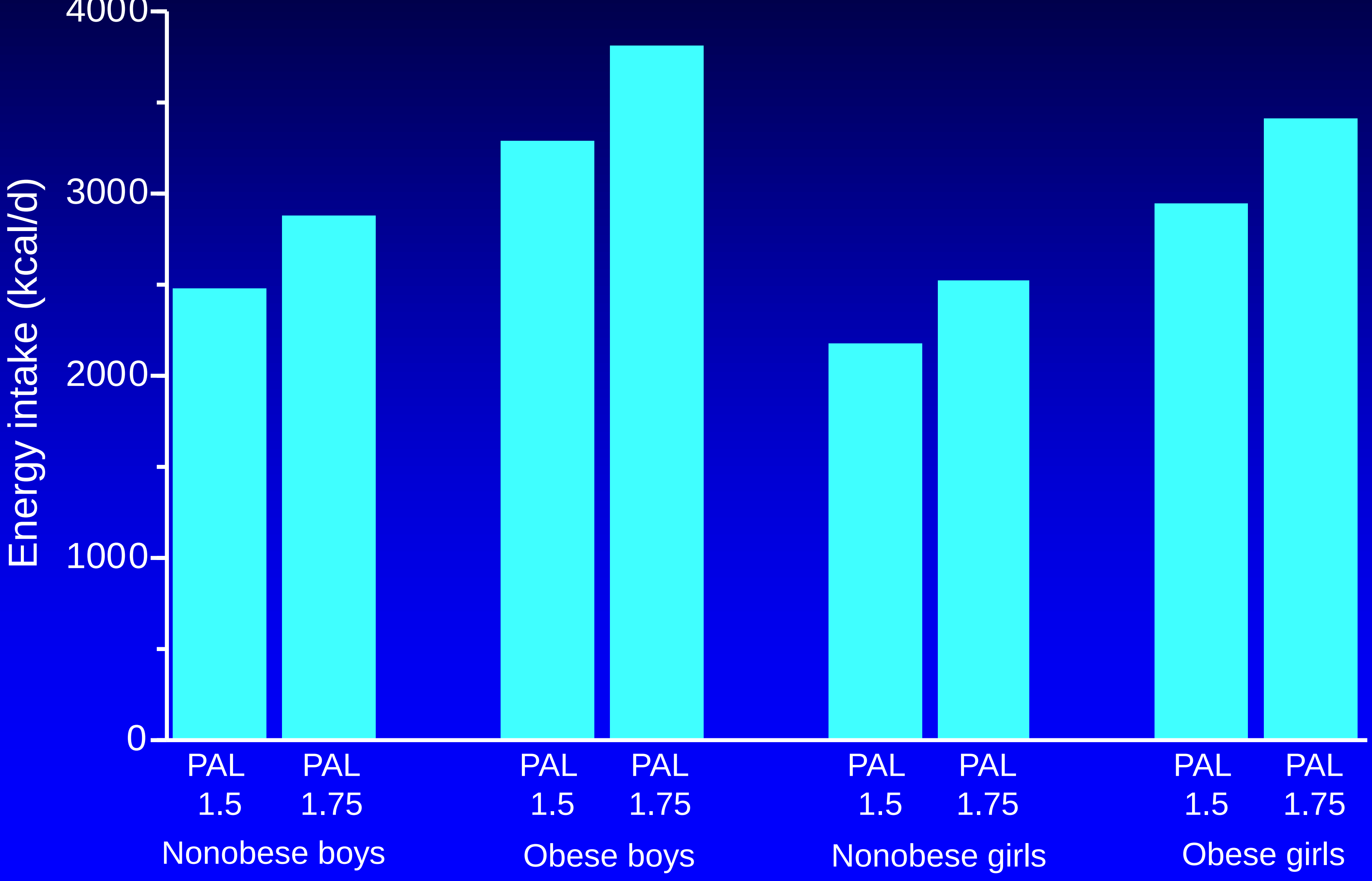
2. Total energy intake in 1 year with increase body mass:

$$EI_{cost,year} = (\Delta C + CE + EE_{year}) / 0.9$$

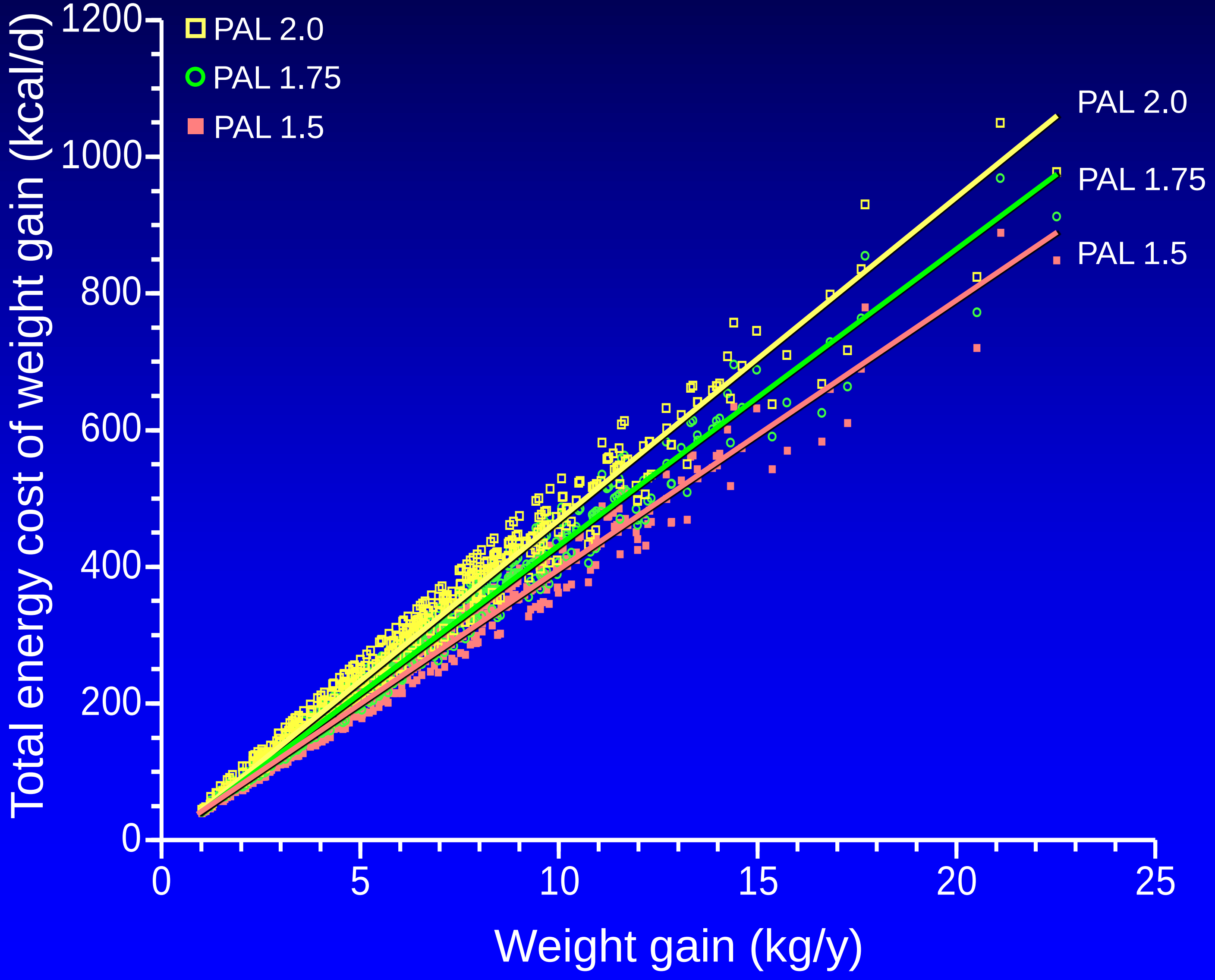
Predicted Total Energy Cost of Weight Gain



Predicted Total Energy Intake



Total Energy Cost of Weight Gain



Physical Activity Factors (PAL) during 1-y Period to Support Weight Gain

	Boys		Girls	
	Nonobese	Obese	Nonobese	Obese
PAL (t=0 y)	1.43	1.41	1.44	1.43
PAL (t=0.25 y)	1.41	1.38	1.41	1.37
PAL (t=0.5 y)	1.37	1.33	1.38	1.34
PAL (t=1.0 y)	1.30	1.25	1.33	1.27

*Median (10^{th} – 90^{th} percentile)

Steady state is chosen at PAL_0 = 1.5

Findings

1. Specific basal energy expenditure for *FFM* (*effm)* depends on gender and Tanner stage.
2. Fraction of fat in new tissue (*fr*) depends on gender and Tanner stage, not *BM*, BMI status or rate of weight gain.
3. Median energy imbalance required to produce observed 1-yweight gains:
   244 (93-448) kcal/d at *PAL*=1.5
   267 (101-485) kcal/d at *PAL*=1.75
4. Energy storage equal to 24-36% of total energy cost of weight gain.
5. If physical activity is constant, total energy intake to result in 1-y weight gains:
   2695 (1890-3730) kcal/d at PAL=1.5
   3127 (2191-4335) kcal/d at *PAL*= 1.75
6. If energy intake is constant, decrease in physical activity to result in 1-y weight gains:
   PAL drops 0.22 (0.08-0.34) units over 1-y
   Equivalent 60 (18-105) min/d walking 2.5 mph

Conclusion

- The total energy cost of weight gain is substantially higher than estimates which do not integrate energy needs over time and thus ignore the energy required to support the increased *BM*.
- The obligatory total energy intake or decline in physical activity required for weight gain is also substantially greater than estimated energy requirements for the development of childhood obesity.

Modelling Weight Loss in Extremely Obese Adolescents in Response to Roux-en-Y Gastric Bypass Surgery

TEENERGY Study

Study Objective:

- To investigate energetic responses to RYGB surgery in extremely obese adolescents, ages 13-19 y.

Specific Aims:

- To monitor changes in weight and body composition using a multicomponent model.
- To measure changes in 24-h total energy expenditure and fuel utilization using room respiration calorimetry.
- To measure changes in free-living energy intake, TEE and PAL using 24-h diet recalls, and heart rate/accelerometer monitoring.
- To predict energy intakes associated with changes in body weight and body composition and adaptations in energy expenditure using the Hall Mathematical Model

TEENERGY Study

Subjects:

- Extremely obese adolescents opting for RYGB surgery or self-management (controls)

Inclusion criteria:

- Ages of 13 to 18 y
- Tanner stage IV or V
- BMI≥50 or BMI≥40 with serious comorbidities such as T2D, obstructive sleep apnea, or pseudotumor cerebri, hypertension, dyslipidemia, nonalcoholic steatohepatitis

Repeated measures design:

- Studied at baseline, and 1.5 and 6 months post-surgery

TEENERGY Study

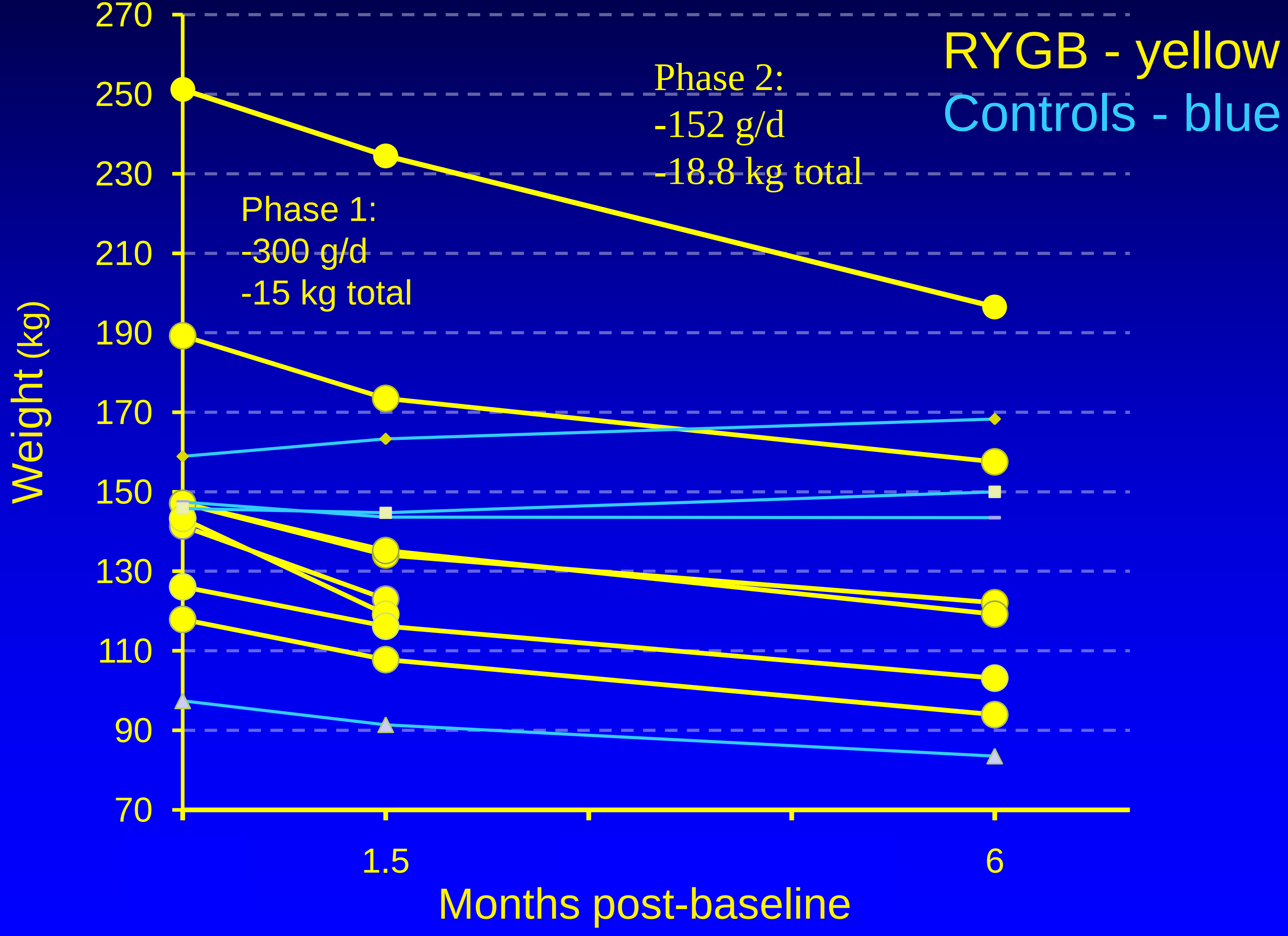
Anthropometry:	Weight, height, circumferences
Body composition:	Total body water by deuterium dilution
	Body density by air displacement plethysmorgraphy (BodPod)
Energy expenditure:	24-h calorimetry
Dietary intake:	24-h multiple-pass diet recall
Physical activity/TEE:	7-d Actiheart monitoring
Modelling:	Cross-sectional Times Series Model
	Hall Mathematical Model of Human Metabolism

Baseline Anthropometry and Body Composition

	RYGB	Controls
N	8	4
Age (y)	16.6 ± 1.1*	14.5 ± 1.1
Sex (M/F)	1/7	2/2
Race/ethnicity (W/B/H)	2/3/3	0/4/0
Weight (kg)	157 ± 43*	136 ± 31
BMI (kg/m^2)	58 ± 12	50 ± 11
Waist circum (cm)	137 ± 22	125 ± 22
TBW (kg)	54 ± 10	50 ± 6
FFM (kg)	72 ± 14	67 ± 8
FM (kg)	86 ± 30	68 ± 24
FM (%)	54 ± 4	49 ± 8

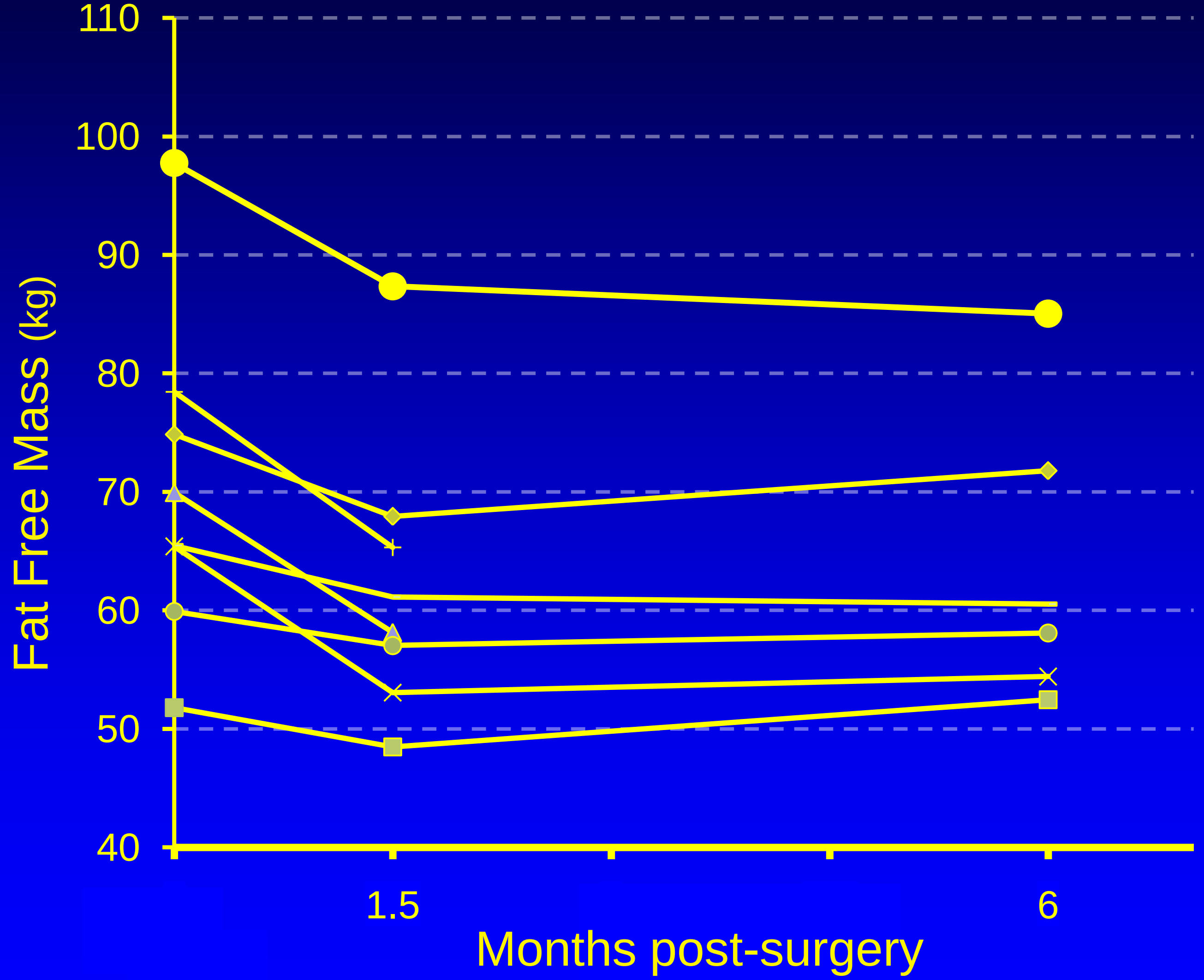
*Mean ± SD

Body Weight

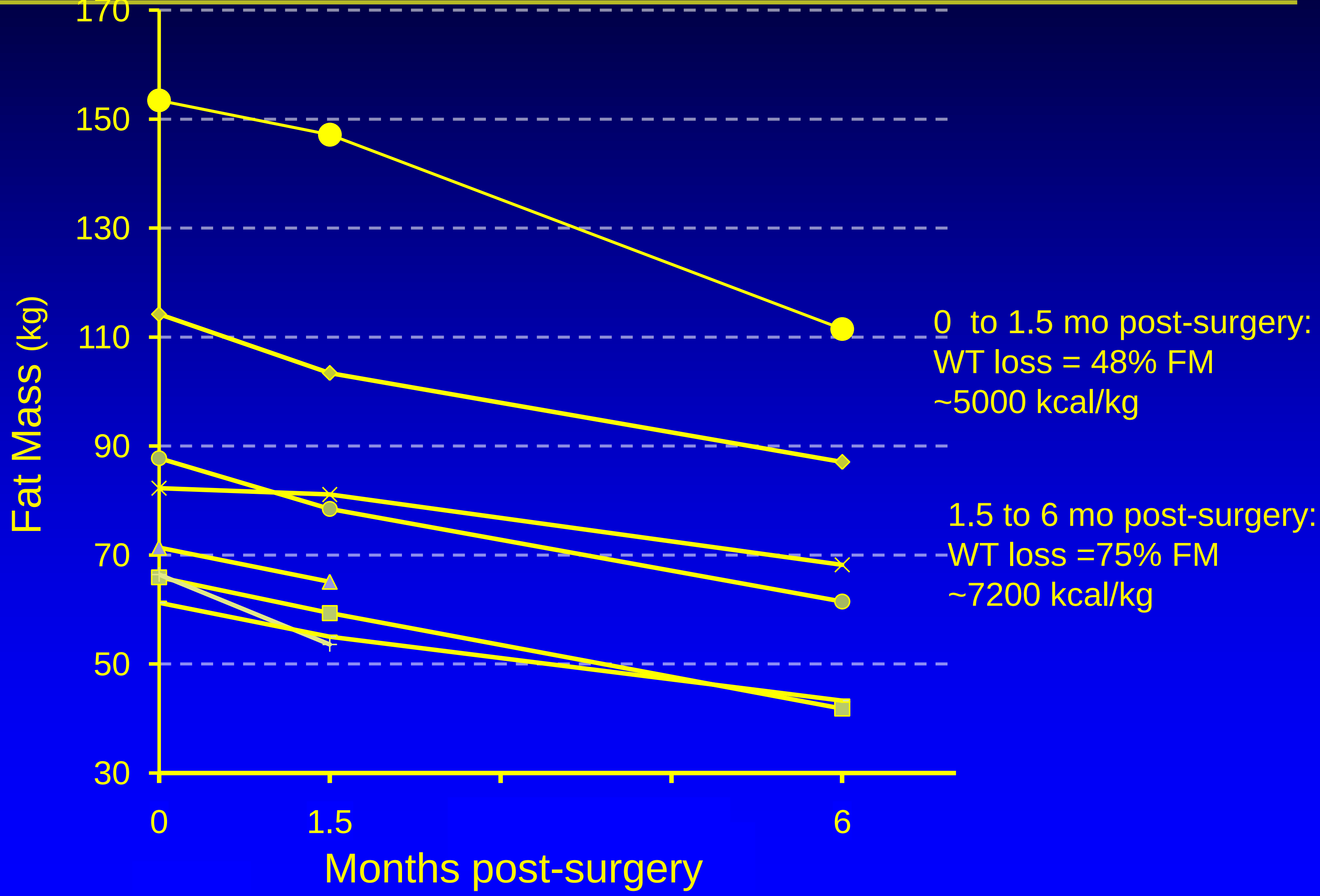


RYGB - yellow
Controls - blue
Phase 1:
-300 g/d
-15 kg total
Phase 2:
-152 g/d
-18.8 kg total
270
250
230
210
190
170
150
130
110
90
70
Weight (kg)
1.5
6
Months post-baseline

RYGB: Fat Free Mass



RYGB: Fat Mass

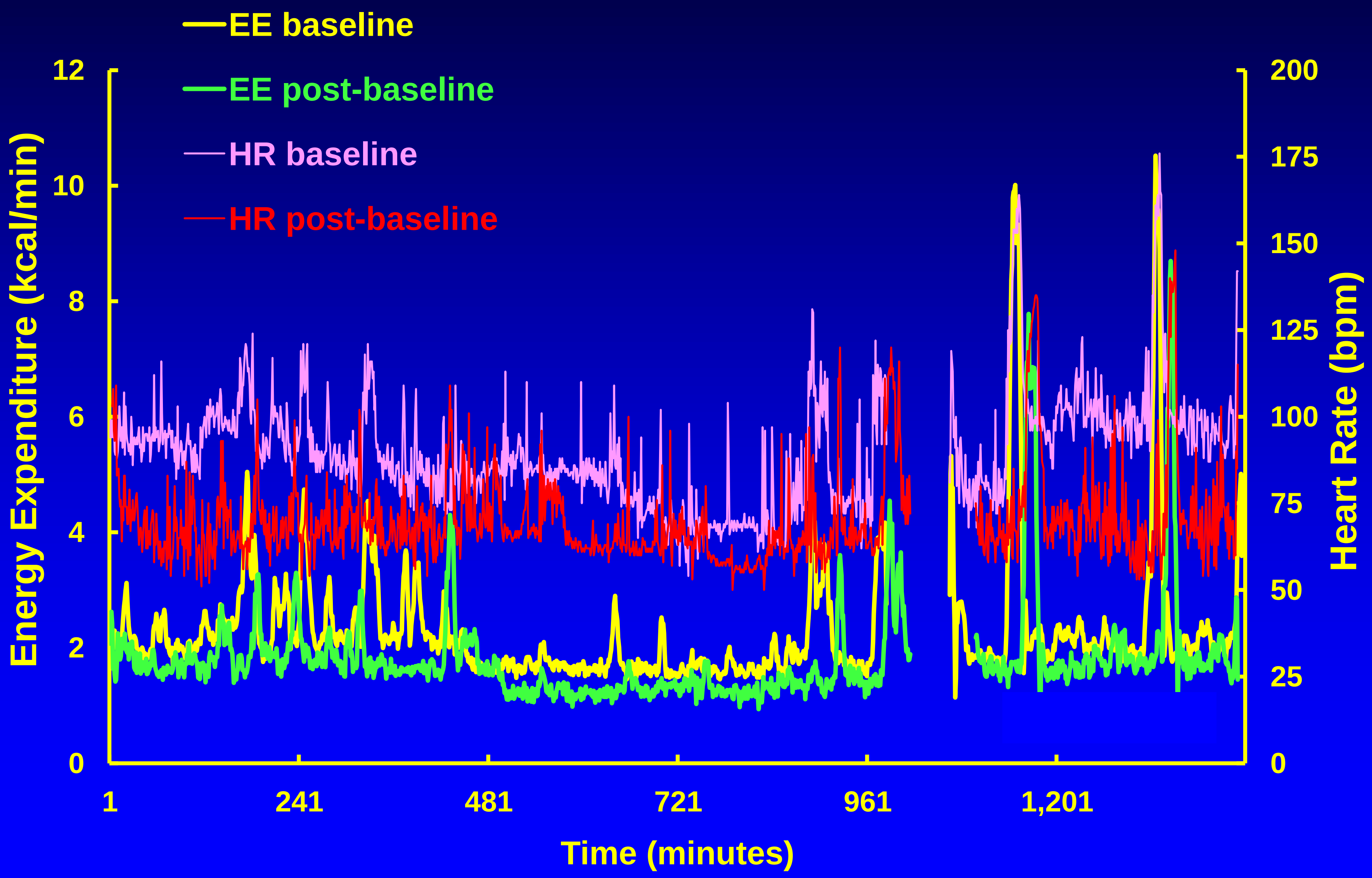


CNRC Respiration Room Calorimeters

Calorimeter Protocol

4:00 pm	Begin
5:30 pm	Dinner
11:00 pm	Lights out
7:30 am	BMR
8:30 am	Blood draw
9:00 am	Breakfast
10:30 am	Treadmill walk
12:00 pm	Lunch
2:00 pm	Treadmill walk
3:00 pm	Snack
4:00 pm	End

24-h Energy Expenditure and HR

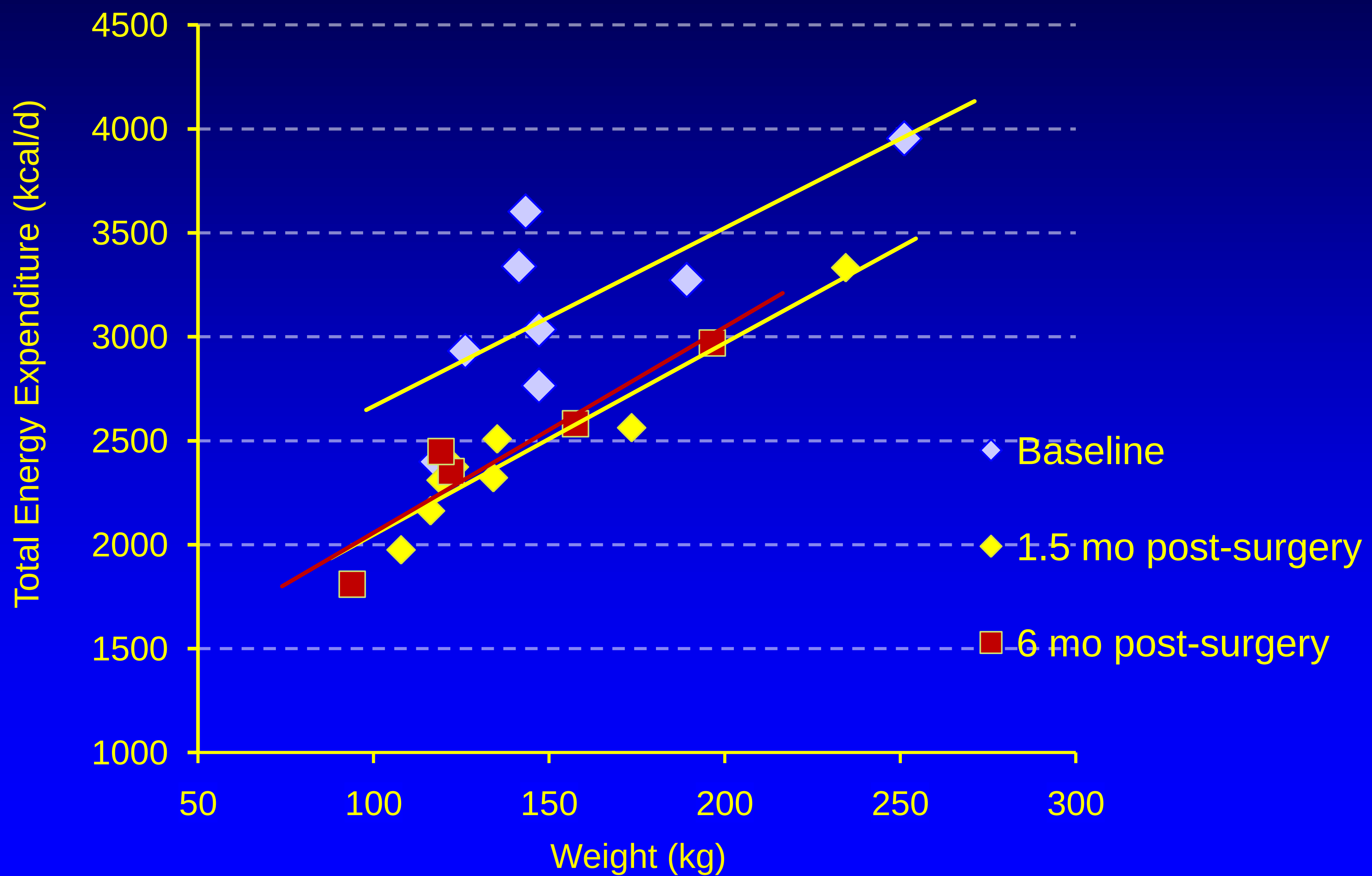


RYGB: 24-h Calorimetry

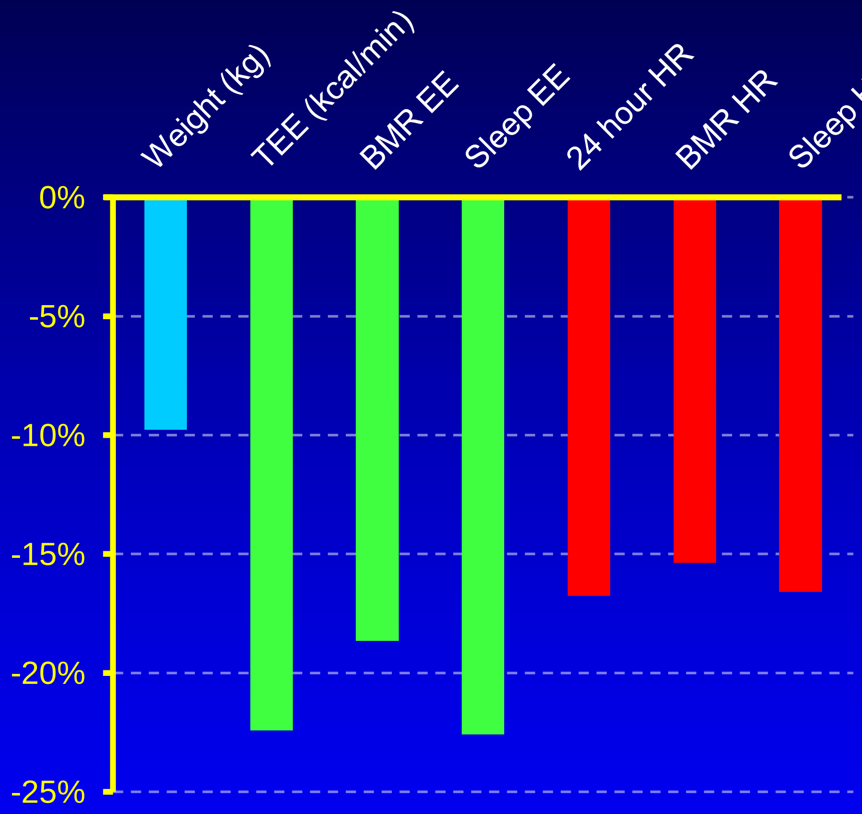
	Baseline	1.5 mo	6 mo
TEE (kcal/d)	3162 ± 489*	2444 ± 404	2433 ± 420
BMR (kcal/d)	2309 ± 389	1872 ± 354	1809 ± 274
Sleep EE (kcal/min)	1.56 ± 0.29	1.20 ± 0.21	1.16 ± 0.17
PAL (TEE/BMR)	1.38 ± 0.06	1.32 ± 0.10	1.34 ± 0.11
RQ	0.85 ± 0.02	0.78 ± 0.01	0.83 ± 0.03

*Mean ± SD

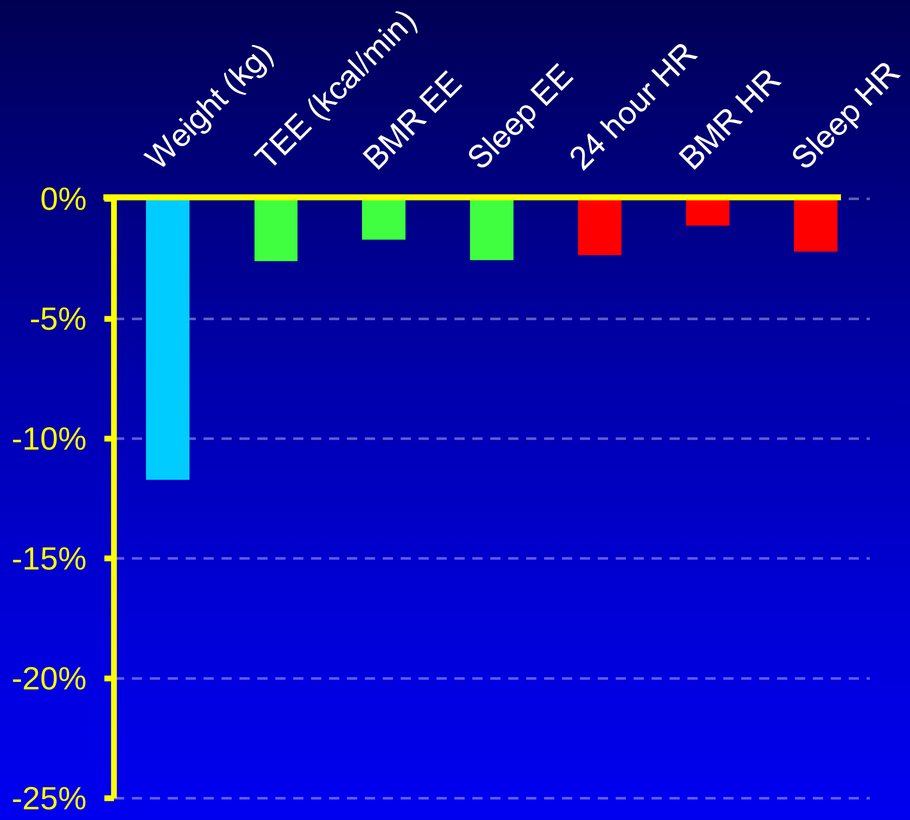
RYGB: Total Energy Expenditure vs. Weight



RYGB: Percent Change in Weight, Energy Expenditure and HR

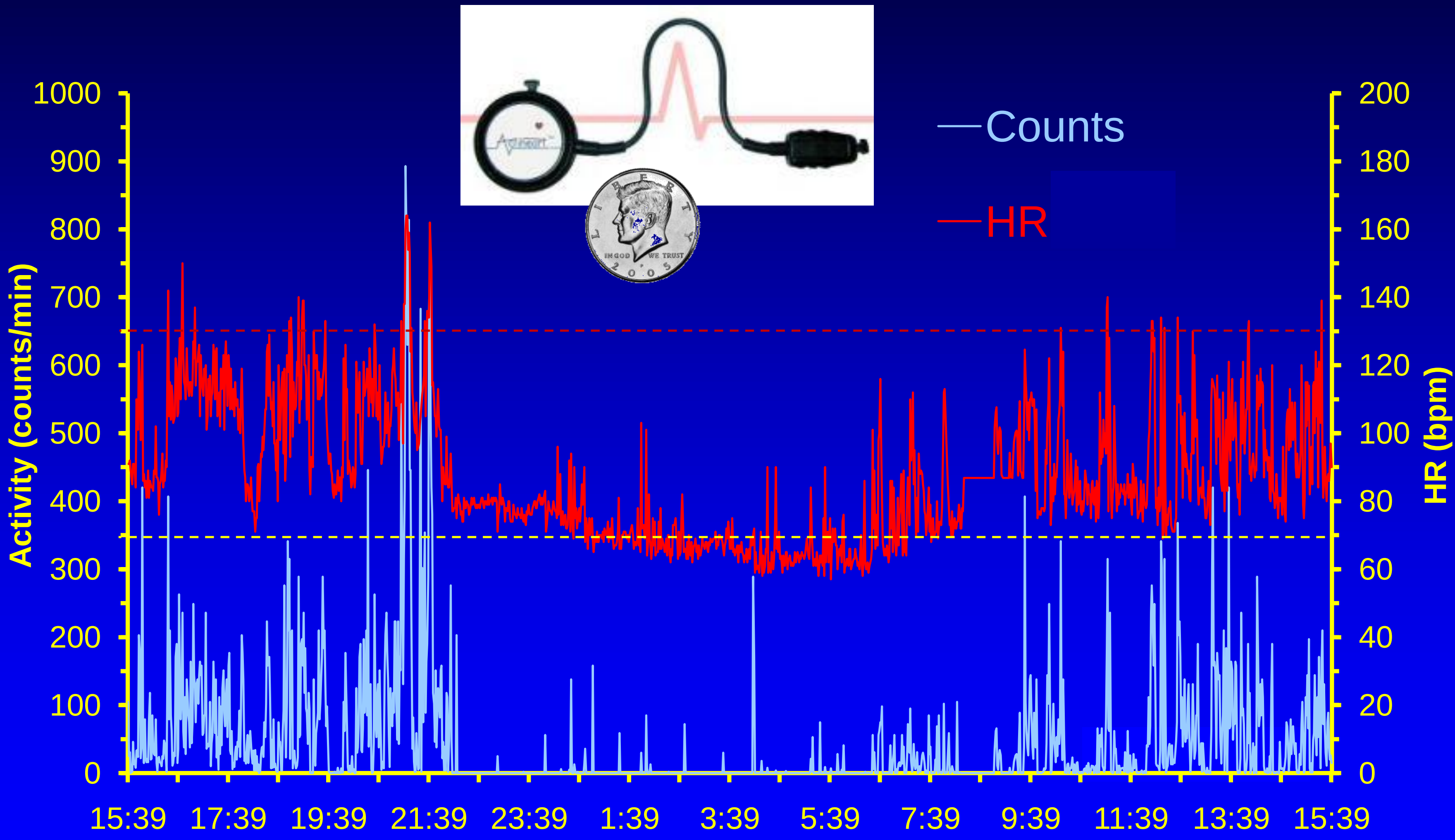


Percent change from baseline to 1.5 month post-surgery



Percent change from 1.5 month post-surgery to 6 months post surgery

7-d Physical Activity and HR Monitoring



Cross-sectional Time Series (CSTS) Modelling

- CSTS is a parametric method that examines multiple subjects (cross-sectional) and how they change over the course of time (longitudinal).
- Any series of values of a variable taken at successive times or in a fixed order.
- CSTS is well suited to describe the dynamic series of minute-by-minute EE, taking into account the correlation structure of the data.

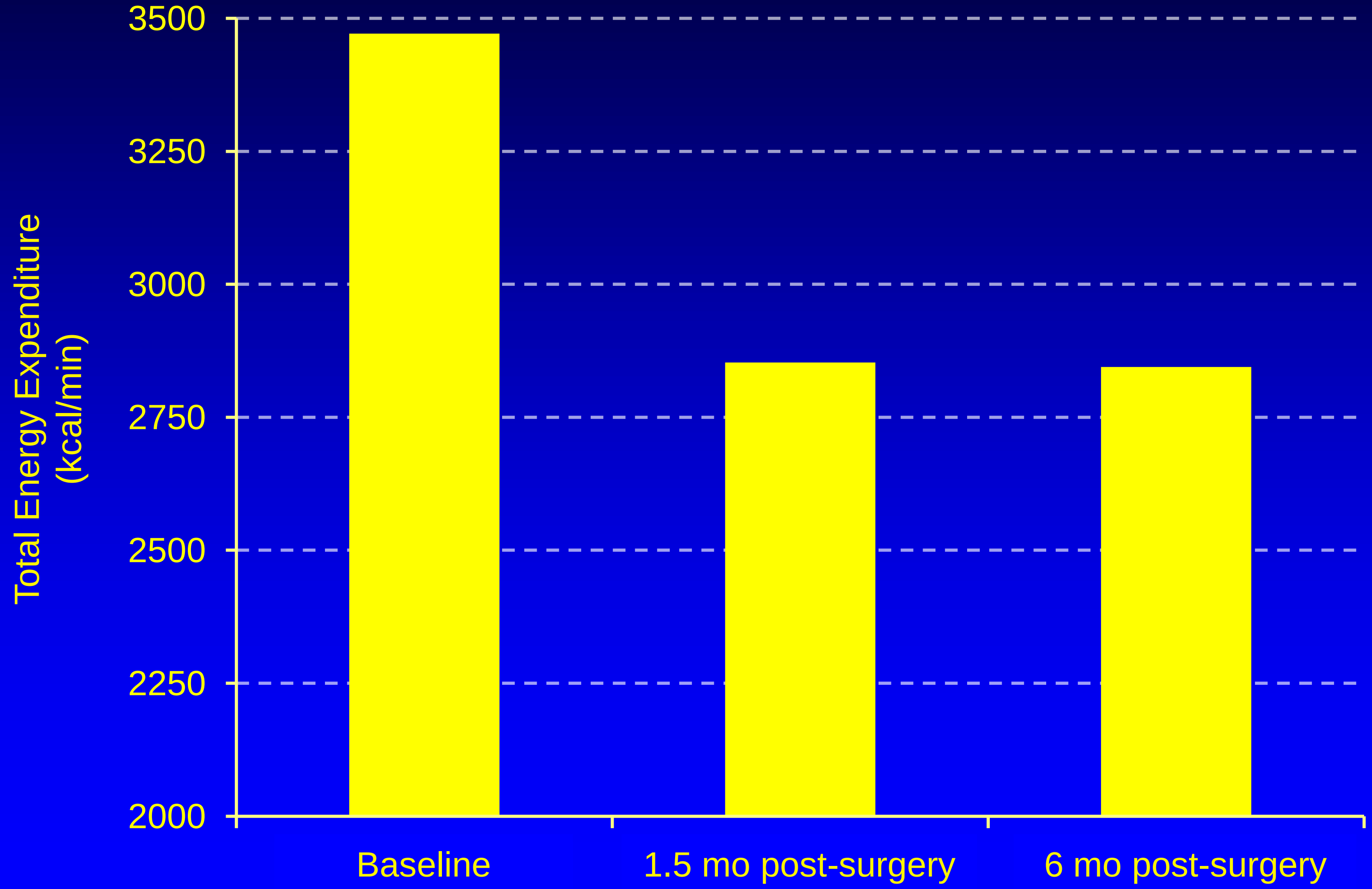
CSTS Model

CSTS model with random intercepts and random slopes

- Time varying variables: HR, HR^2, 1-period and 2-period lagged and lead values of HR
- Time varying variables: PA, PA^2, and 1-period and 2-period lagged values of PA
- Subject characteristics: age, age^2, gender, weight, height, minimum HR, sitting HR
- Interaction terms: HR × height, HR × weight, HR × Age, HR × gender, PA × weight and PA × gender
- Validated against calorimeter data: error 0.2±7.5%

Zakeri, J Appl Physiol 2008

7-d Mean Total Energy Expenditure

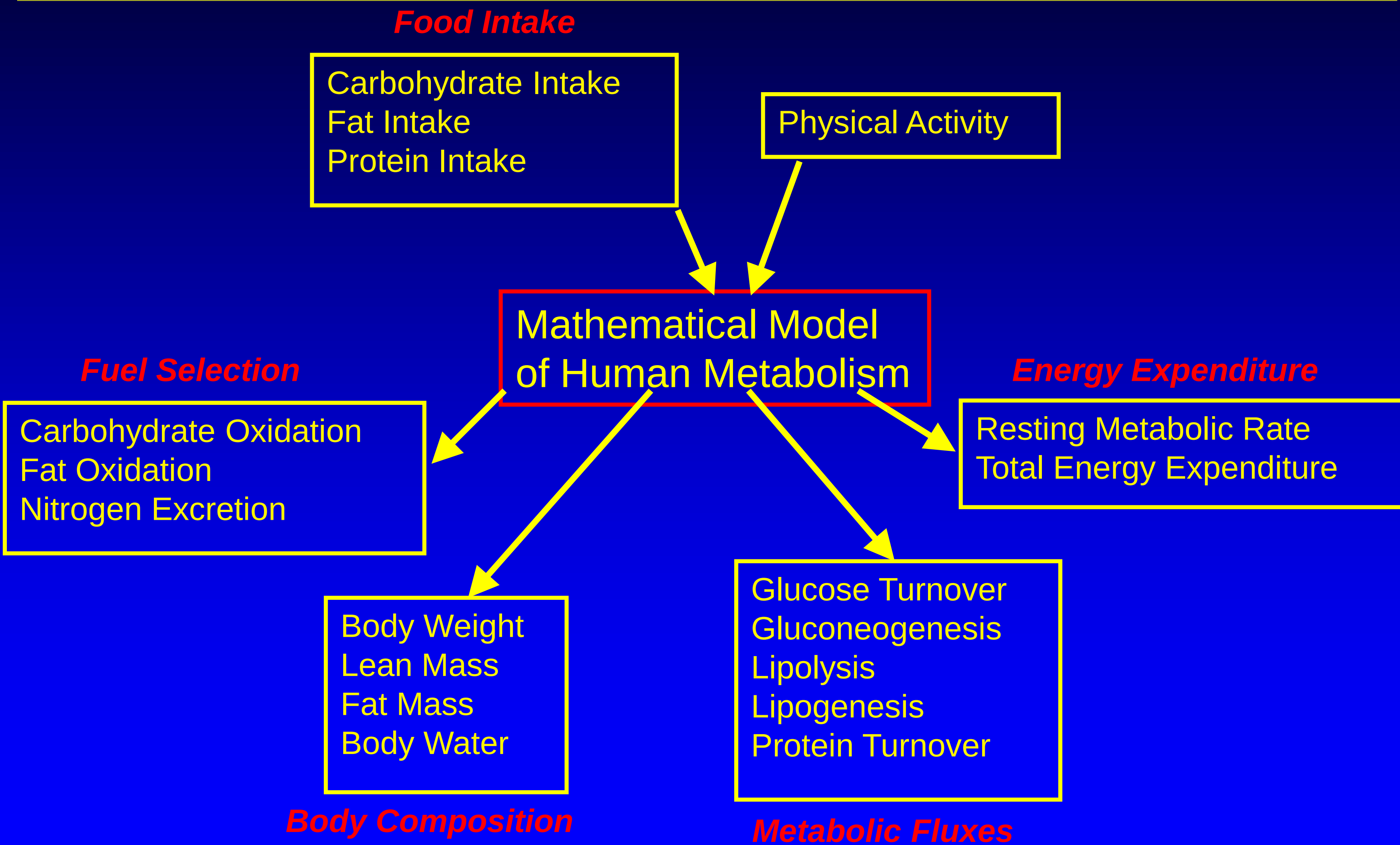


Hall Mathematical Model of Human Metabolism

- Based on specified initial conditions, model simulates how diet perturbations result in adaptations in energy expenditure and fuel selection giving rise to changes of body weight and composition.
- Based on law of energy conservation, such that body composition changes result from imbalances between the energy intake and energy utilization.
- Composed of 8 ordinary differential equations, quantitatively tracks the metabolism of all three dietary macronutrients.

Hall KD. Am J Physiol Endocrinol Metab 2010;298:E449-E466.

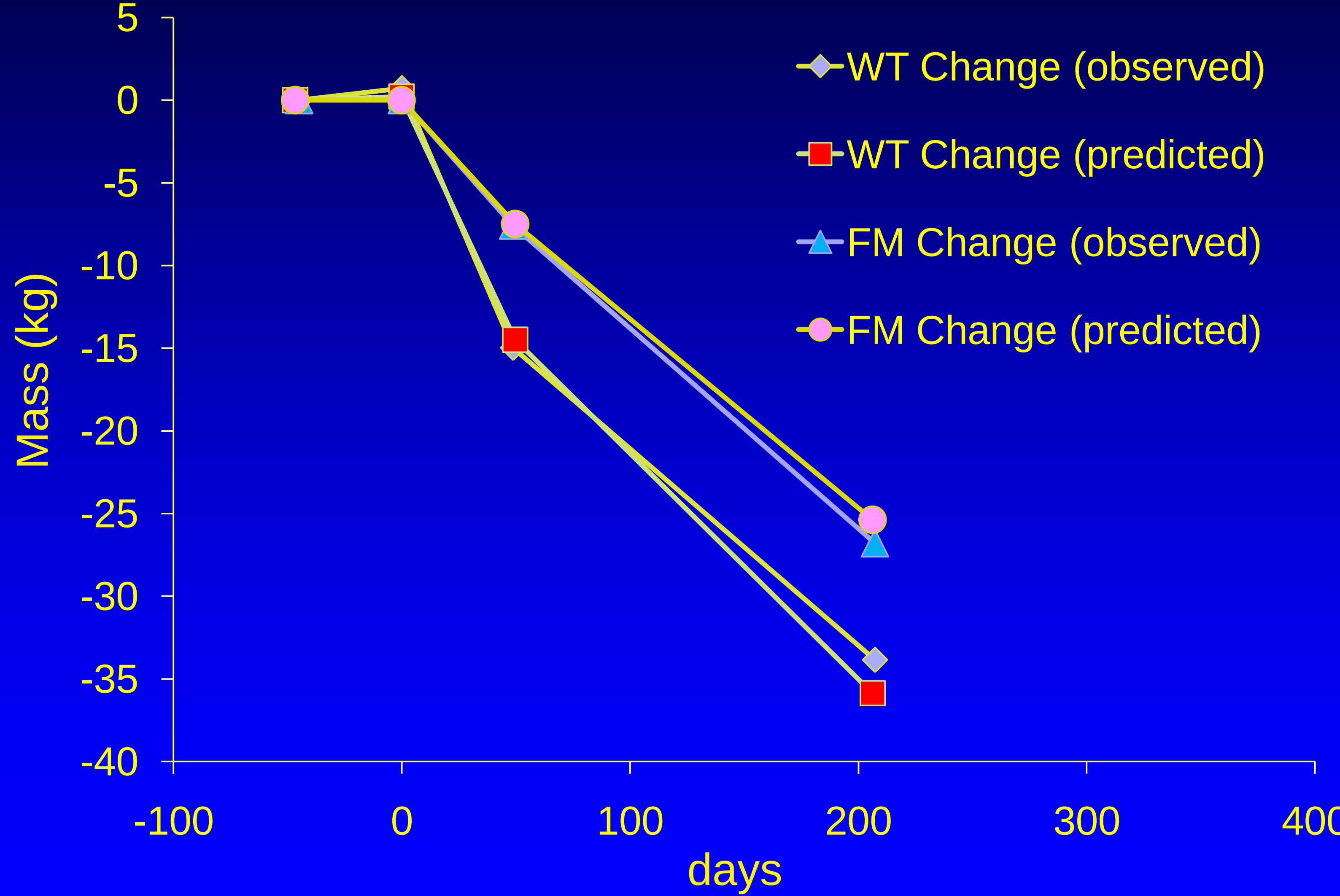
Quantitative Data Integration



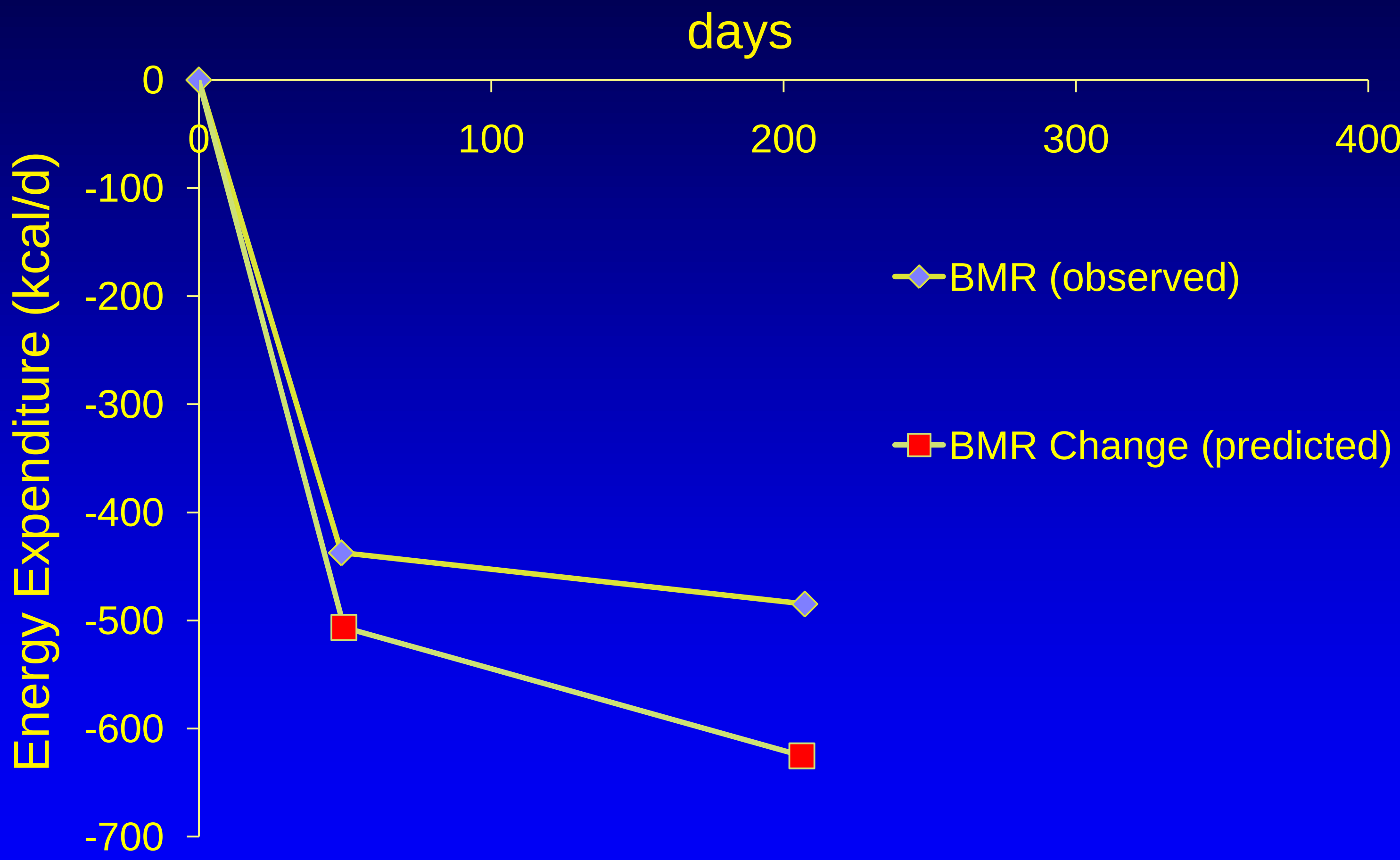
KD Hall. *Am J Physiol* 298: E449–66 (2010)

NIDDK

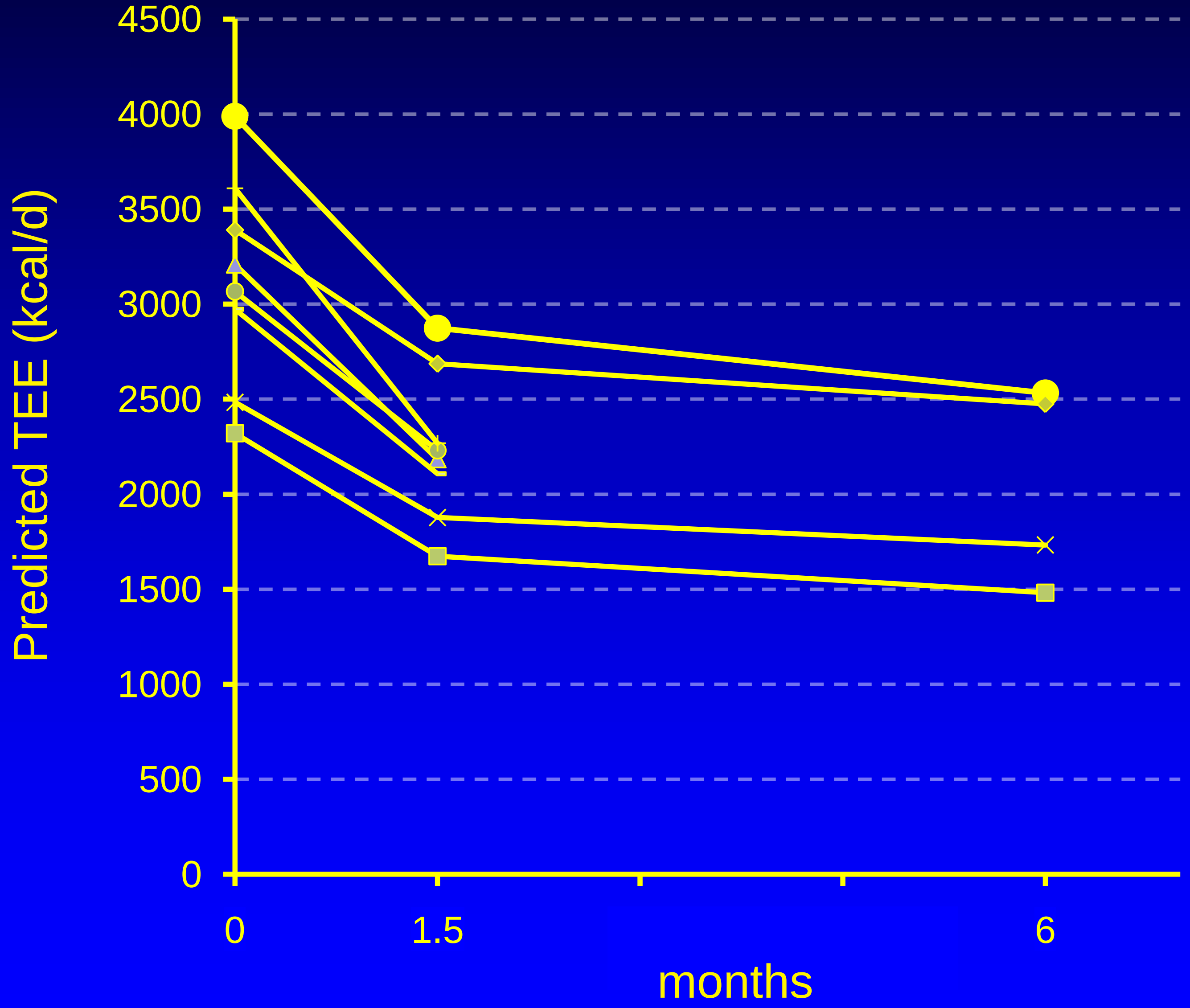
Hall Model:
Predicted vs. Observed Weight and FM



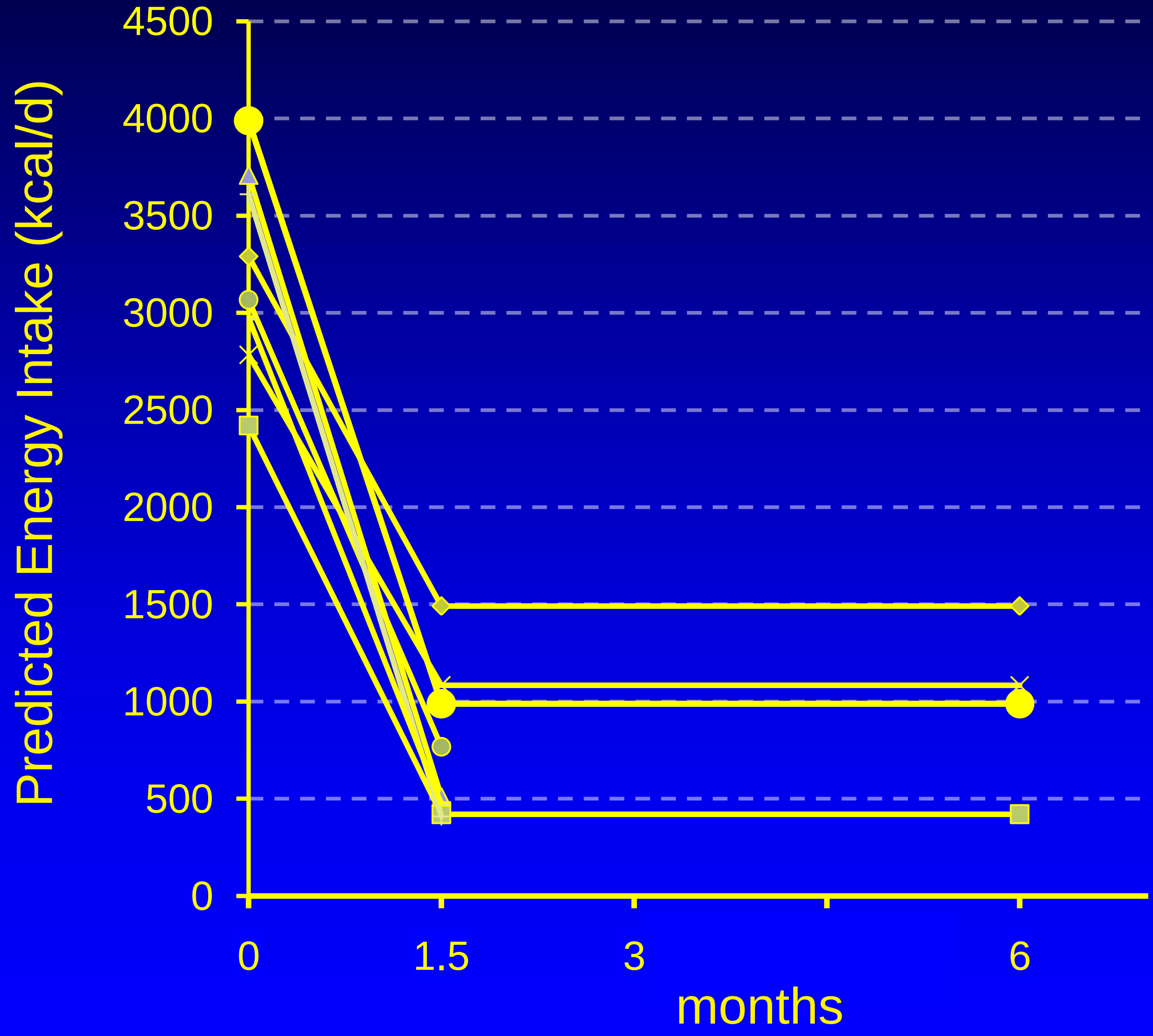
Hall Model:
Predicted vs. Observed BMR



Hall Model: Predicted TEE



Hall Model: Predicted Energy Intake



Hall Model: Predicted vs. Observed

	Pre-surgery		1.5 mo post-surgery		6 mo post-surgery	
	Model	Observed	Model	Observed	Model	Observed
WT (kg)	158*	158	143	143	140	142
FM (kg)	88	86	80	80	79	77
RMR (kcal/d)	2309	2309	1803	1872	1644	1784
PAL	1.38†	1.38† 1.51‡	1.32†	1.32† 1.46‡	1.34†	1.34† 1.61‡
TEE (kcal/d)$^{+}$	3130	3163† 3471‡	2238	2442† 2853‡	2056	2454† 2845‡
EI (kcal/d)	3231	1713	768	499	996	903

*Mean
†Calorimeter
‡CSTS

Summary: Preliminary Results

- RYGB induced substantial weight loss equivalent to 20% initial weight in 6 months.
- Weight loss was associated with an initial fall in FFM and a linear decline in FM.
- Energetic adaptations and a shift towards fat oxidation occurred early and persisted at 6 months.
- RYGB induced substantial declines in free-living energy intake and TEE.
- Hall Mathematical Model accurately predicts changes in weight, fat mass and RMR that are used to predict TEE and energy intake.

Modelling Challenges

1. Further develop weight gain/loss model in children and adolescents (one or two models?)

2. Methods to infer physical activity levels

4. Determine the accuracy and precision of models for groups vs. individuals

5. Develop practical clinical tools for counseling families on diet, EE, and expected weight gain/loss

Acknowledgments

VIVA and TeEnergy

Study participants

Co-investigators

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