Calories, Carbs, or Quality?
What Matters Most for Body Weight

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National Institutes of Health

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Wrong, Wrong, Wrong!

If a patient reduces caloric intake by 500 calories per day for 7 days and loses about 1 lb of body weight per week, it would take approximately 52 weeks to achieve a 50 lb weight loss.
Erroneous Weight Loss Projections

3500 kcal per lb rule
Calories In & Out are NOT Independent
Feedback Regulation of Body Weight

Calories Out

Leptin, etc.

Calories In

5

5
Mathematical Modeling of Metabolism

\[ \rho_c \frac{dG}{dt} = CI - DNL + GNG_p + GNG_F - G3P - CarbOx \]

\[ \rho_F \frac{dF}{dt} = 3M_F FM/M_TG + \varepsilon_d DNL - KU_{exc} - (1 - \varepsilon_k)KTG - FatOx \]

\[ \rho_p \frac{dP}{dt} = PI - GNG_p - ProtOx \]

\[ FFM = BM + ECF + ECP + LCM = BM + ECF + ECP + ICW + P + G + ICS \]

\[ = BM + ECF + ECP + ICW + P(1 + h_p) + G(1 + h_G) + ICS \]

\[ \frac{dECF}{dt} = \frac{1}{[Na]} \left( \Delta N_{d_{diet}} - \xi_{Na} (ECF - ECF_{init}) - \xi_{CI} (1 - CI/Cl_b) \right) + \Delta ECF \]

\[ \tau_{BW} \frac{d\Delta ECF}{dt} = \xi_{BW} (BW - BW_{init}) - \Delta ECF \]

\[ TEE = TEF + PAE + RMR \]

\[ RMR = E_c + \gamma_{BF} M_B + \gamma_{FFM} FFM - M_B - \Delta G(1 + h_g) - (ECF - ECF_{init}) + \gamma_{EF} F \]

\[ + (1 - \varepsilon_d) DNL + (1 - \varepsilon_g)(GNG_F + GNG_P) + (1 - \varepsilon_K)KTG \]

\[ + \eta_N N_{exc} + (\eta_p + \varepsilon_p)D_p + \eta_p \frac{dP}{dt} + \eta_p D_F + \eta_F \frac{dF}{dt} + \eta_G D_G + \eta_G \frac{dG}{dt} \]

\[ \tau_i \frac{dT}{dt} = \begin{cases} \lambda_1 (\Delta EI/EI_b) - T, & \text{if } EI < EI_b \\ \lambda_2 (\Delta EI/EI_b) - T, & \text{else} \end{cases} \]

\[ \hat{F}_{FFM} = \sum_i \gamma_i \frac{dM_i}{dFFM} \]

\[ CarbOx = GNG_F + GNG_p - G3P + f_C \times \bar{TEE} \]

\[ FatOx = KetOx + f_F \times \bar{TEE} \]

\[ ProtOx = f_p \times \bar{TEE} \]

\[ TEF = \alpha_F FI + \alpha_p PI + \alpha_C CI \]

\[ D_p = \hat{D}_p \left( \frac{P}{P_{Keys}} + \chi \left( \frac{AP}{PI_b} \right) \right) \]

\[ D_F = \hat{D}_F \left( \frac{F}{F_{Keys}} \right)^2 \left[ L_{diet} + L_{PA} \right] \]

\[ \tau_{L_{diet}} = \frac{K_S}{L_{diet}} \left[ 1 + (A_L - B_L) \exp(-k_L CI/Cl_b) + B_L \right] \]

\[ GNG_F = F(\rho_c M_G) + D_F \rho_c \frac{M_G}{M_TG} \]

\[ L_{PA} = \psi \left( \frac{D + \nu}{D_{init} + \nu_{init}} - 1 \right) \]

\[ KTG = \rho_K D_F \left[ \frac{D_F/\hat{D}_F}{K + D_F/\hat{D}_F} \right] \exp\left( -k_p PI_b \right) \exp\left( -k_g \frac{G}{G_{init}} \right) \]

\[ KU_{exc} = \begin{cases} \rho_K KU_{max} (KTG/\rho_K - KTG_{thresh})/(KTG_{max} - KTG_{thresh}), & \text{if } KTG/\rho_K < KTG_{thresh} \\ 0, & \text{else} \end{cases} \]

\[ f_C = w_G \left( G/\hat{G} \right) + w_C \max \left\{ 0, 1 + \left( S_C \Delta CI/Cl_b \right) \right\} G/(G_{min} + G) \]

\[ f_F = \frac{w_F \left( D_F/\hat{D}_F \right)}{Z} \]

\[ f_p = \frac{w_p \max \left\{ 0, 1 + P_{sig} \right\} \left( D_p/\hat{D}_p \right) S_A \exp\left( -k_A (\delta + \nu) / (\delta_b + \nu_b) \right)}{Z} \]

\[ \tau_{PI} \frac{dP_{sig}}{dt} = S_p \Delta PI/PI_b - P_{sig} \]
Mathematical Modeling of Metabolism

Baseline
Demographics & Anthropometrics

Physical Activity
Food Intake

Mathematical Model of Human Metabolism

Body Weight
Body Fat

Corrected Weight Loss Projections

Dynamic Model

3500 kcal per lb rule

Feedback Control of Appetite?

Calories Out → Leptin, etc.

Calories In → Leptin, etc.
The fundamental flaw in obesity research

J. T. Winkler

obesity reviews (2005) 6, 199-202

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How often, in the past 3 months, did you eat the following?

<table>
<thead>
<tr>
<th>Food Type</th>
<th>Never</th>
<th>Less than 1 time per week</th>
<th>1-3 times per week</th>
<th>4-6 times per week</th>
<th>6 times per week or more</th>
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</thead>
<tbody>
<tr>
<td>Fruit (apples, bananas, oranges, etc.)</td>
<td>1/2 cup raw fruit; 1/2 medium apple or large orange</td>
<td>1/2 cup cooked or raw; 1 carrot or stalk celery</td>
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<td>Vegetables (carrots, mushrooms, potatoes, etc.)</td>
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<tr>
<td>Chicken (fried chicken, in soup, grilled chicken, etc.)</td>
<td>3-4 oz; 1/2 large or 1 small breast; 2 drumsticks</td>
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<tr>
<td>Turkey (turkey dinner, turkey sandwich, in soup, etc.)</td>
<td>3-4 oz; 6-8 very thin slices; 1-3 thick slices</td>
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<tr>
<td>Fish and Seafood (tuna, shrimp, crab, etc.)</td>
<td>3-4 oz; 1 can of tuna; 5 medium shrimp</td>
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<tr>
<td>Pork (ham, pork chops, ribs, etc.)</td>
<td>3-4 oz; 1 pork chop, 2 ribs; 3-4 slices bacon</td>
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<tr>
<td>Beef (steak, meatballs, in tacos, etc.)</td>
<td>3-4 oz; 1/2 lb burger; 3-6 slices roast beef</td>
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<tr>
<td>Other Meat (duck, lamb, venison, etc.)</td>
<td>3-4 oz; a piece about the size of your palm</td>
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<td>Nuts (almonds, cashews, walnuts, etc.)</td>
<td>1/4 cup or 1 handful; 20 almonds; 2 tbsp nut butter</td>
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<td>Beans (tofu, chickpeas, chill, etc.)</td>
<td>1/2 cup cooked beans; 1/4 cup hummus or tofu</td>
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<td>Dairy (cheese, milk, yogurt, etc.)</td>
<td>3 slices cheese; 1 cup milk; 1 cup yogurt</td>
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<td>Eggs (omelet, in salad, in baked goods, etc.)</td>
<td>1 egg; 1/4 cup scrambled eggs or 1/2 cup egg salad</td>
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<tr>
<td>Grains (bread, pasta, rice, etc.)</td>
<td>1 slice bread or pizza; 1/2 cup rice or pasta</td>
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<td>Sweets (candy, cookies, pie, etc.)</td>
<td>2 small cookies; 1 slice cake or pie</td>
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<tr>
<td>Caffeinated Soft Drinks (cola, diet cola, energy drinks, etc.)</td>
<td>1 can (12 oz) soda; small fountain drink</td>
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<tr>
<td>Coffee and Tea (hot coffee, iced coffee, black tea, etc.)</td>
<td>6 oz hot coffee or tea; small iced coffee</td>
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24 HOUR RECORD

<table>
<thead>
<tr>
<th>Time</th>
<th>Quantity eaten</th>
<th>Details of food and drink</th>
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<tbody>
<tr>
<td>7:30 am</td>
<td>1 Cup</td>
<td>Tea</td>
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<tr>
<td>1/2 tsp</td>
<td>Semi-Skimmed Milk</td>
<td></td>
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<tr>
<td>1 1/2 tsp</td>
<td>White Sugar</td>
<td></td>
</tr>
<tr>
<td>1 tsp</td>
<td>Rice Crispies &amp; Sliced Banana</td>
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<tr>
<td>2 tsp</td>
<td>White Sugar</td>
<td></td>
</tr>
<tr>
<td>4 am</td>
<td>1 Mug</td>
<td>Instant Powdered Coffee</td>
</tr>
<tr>
<td>1 1/2 tsp</td>
<td>White Sugar</td>
<td></td>
</tr>
<tr>
<td>2 1/2 tsp</td>
<td>Semi-Skimmed Milk</td>
<td></td>
</tr>
<tr>
<td>6 1/2 tsp</td>
<td>Water</td>
<td></td>
</tr>
<tr>
<td>11:30 am</td>
<td>1 Big Plate</td>
<td>Homemade Steamed &amp; Vegetables (Boiled)</td>
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<tr>
<td>3 1/2 tsp</td>
<td>Peanut Butter</td>
<td>(Fresh)</td>
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<tr>
<td>2 tsp</td>
<td>Carrots</td>
<td>(Fresh)</td>
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<tr>
<td>1 glass</td>
<td>Orange Squash</td>
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<tr>
<td>3 pm</td>
<td>1 Cup</td>
<td>Tea</td>
</tr>
<tr>
<td>1 1/2 tsp</td>
<td>Semi-Skimmed Milk</td>
<td></td>
</tr>
<tr>
<td>2 tsp</td>
<td>White Sugar</td>
<td></td>
</tr>
<tr>
<td>2 1/2 tsp</td>
<td>Small Biscuits</td>
<td></td>
</tr>
<tr>
<td>5 pm</td>
<td>1 Medium Size Plate</td>
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<tr>
<td>2 1/2 tsp</td>
<td>Sliced Bread (Fried)</td>
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<tr>
<td>1 tsp</td>
<td>White Bread</td>
<td></td>
</tr>
<tr>
<td>1 1/2 tsp</td>
<td>Non-Fat Butter (Willow)</td>
<td></td>
</tr>
<tr>
<td>9:30 pm</td>
<td>1 Big Cup</td>
<td>Drinking Chocolate</td>
</tr>
<tr>
<td>1 1/2 tsp</td>
<td>White Sugar</td>
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Math Models to Calculate Calorie Intake?

Baseline Demographics & Anthropometrics

Calorie Intake

Mathematical Model of Human Metabolism

Calorie Expenditure

Body Weight

Body Fat

Validation: Caloric Restriction for 2 Years

Body Weight (kg) vs. Time (weeks)

DLW+DXA measurements

N=140

Mean ± 95% CI

Mean CALERIE 2 Energy Intake Changes

Model vs DLW/DXA within 40 kcal/d

How to Increase Calorie Expenditure?

Leptin, etc.
How to Increase Calorie Expenditure?

Calories Out

Calories In

~90 g/d glucose

Leptin, etc.

Leptin, etc.
Weight Changes during SGLT2 Inhibition

N=153 adults with Obesity & Type 2 diabetes treated with canagliflozin

Intake Changes during SGLT2 Inhibition

~95 kcal/d per kg BW loss

Feedback Regulation of Body Weight

Leptin, etc.

Lifestyle Induced Weight & Fat Loss

Corresponding Energy Balance Dynamics

Exponential decay of diet adherence?

Mean ± 95% CI

Perceived Effort

Appetite increases ~95 kcal/d per kg weight lost

Large & Persistent Perceived Effort

The Promise of Low Carb Diets
Carbohydrate-Insulin Model of Obesity

Excessive anabolic drive in adipose tissue

"the metabolic effects of carbohydrate [to increase insulin] cause the adipocyte to take in, store, and trap too many calories. Subsequently, energy expenditure declines and hunger increases"

Fat Loss Requires Carbohydrate Reduction?

“Any diet that succeeds does so because the dieter restricts fattening carbohydrates…Those who lose fat on a diet do so because of what they are not eating – the fattening carbohydrates”

Gary Taubes, Why we get fat and what to do about it (2011).
Isocaloric 30% Calorie Restricted Diets

Only RC Diet Decreased Insulin Secretion

N=19 men & women with obesity

24 hr C-peptide (% change)

Mean ± 95% CI

* p<0.01 vs baseline

Only RC Diet Increased Fat Oxidation

N=19 men & women with obesity

Mean ± 95% CI
** p<0.001

More Cumulative Body Fat Loss with RF

Cumulative Fat Change (g)

Time (days)

**N=19 men & women with obesity

Mean ± 95% CI

** p<0.001

Only RC Decreases Energy Expenditure

Recently, a study in *Cell Metabolism* by Kevin Hall from the National Institutes of Health attracted a lot of buzz in the news and online…[but] **there were some real problems with the study**

- The **low-carb diet wasn’t low at all**, actually, with 29 percent of calories coming from carbs, including refined carbs. A true low-carb diet would have less than 10 percent of calories from carbs.
- It was a **very short-duration study (only six days)** conducted on only nineteen people who were contained in a metabolic ward where all the food was provided…It showed what happened in a vacuum but not in real life.

Mark Hyman, MD
*Eat Fat, Get Thin* (2016)
Hypothetical Extended Duration Study

24hr Respiratory Qotient vs Time (days)

Fat Adaptation?
2 Month Isocaloric Ketogenic Diet Study

Day -28  Day -15  Day 0  Day 15  Day 28

4 weeks inpatient Baseline Diet  4 weeks inpatient Low Carb Ketogenic Diet

Energy Intake Adjustment  Energy Intake Clamped

2 days residing in metabolic chamber

DLW dose  DXA

Rapid & Persistent Decrease in Insulin Secretion

N=17 men with overweight and class I obesity

24 hr C-peptide (% change)

Time (days)

Mean ± 95% CI

*p<0.0033

Rapid & Persistent Increase in Ketosis

N=17 men with overweight and class I obesity

24hr Urinary Ketone Excretion (g/d)

Time (days)

Mean ± SEM

Rapid & Persistent Shift to Fat Oxidation

Burning Carbs

N=17 men with overweight and class I obesity

Fat Adaptation?

\[ \Delta 24\text{hr RQ} \]

Time (days)

Mean ± 95% CI

* \( p<0.0045 \)

No Significant Effect on Daily Expenditure

N=17 men with overweight and class I obesity

P = 0.21

Mean ± 95% CI

KD Hall et al. AJCN 104:1488-90 (2016).
Energy Expenditure: Isocaloric Carb vs. Fat


Pooled weighted mean difference

Favors low fat diet
Favors low CHO diet

Weighted Mean Difference in Energy Expenditure (kcal/d)

P < 0.0001

ES (Kcal/d) LCL (Kcal/d) UCL (Kcal/d)

Bandini et al. 1994 -365.0 -479.6 -250.4
Shetty et al. 1994 -38.3 -103.2 26.7
Hall et al. 2016 & 2019 56.6 31.6 81.6
Davies et al. 2001 -50.4 -104.4 3.5
Hall et al. 2015 -48.1 -62.3 -33.9
Verboecket-van de Venne et al. 1994 -65.5 -95.1 -35.9
Verboecket-van de Venne et al. 1996 -55.0 -61.6 -28.2
Hill et al. 1991 -68.6 -121.5 -15.6
Thearle et al. 2013 -80.9 -108.8 -53.0
Hurni et al. 1982 -123.6 -207.2 -40.1
Horton et al. 1995 -94.2 -128.8 -59.5
Schrauwen et al. 2000 -83.7 -230.2 62.8
Bergouignan et al. 2012 -54.3 -102.8 -5.8
Truth et al. 2003 26.4 0.0 52.7
Schrauwen et al. 1997 -79.6 -137.8 -21.5
Roy et al. 1998 4.9 -41.0 50.7
Dirlewanger et al. 2000 -81.3 -128.7 -35.9
Astrup et al. 1994 -45.2 -66.3 -24.2
Shepherd et al. 2001 -166.3 -321.5 -11.1
Eckel et al. 2006 -125.0 -201.1 -48.9
Abbott et al. 1990 68.0 6.3 129.6
Cooper et al. 2009 -20.4 -70.5 29.7
Rumpier et al. 1991 198.0 -192.5 588.5
Ebbeling et al. 2012 159.0 99.2 218.8
McDevitt et al. 2000 -10.0 -36.9 16.9
Goldberg et al. 1998 4.8 -46.1 55.7
Galgani et al. 2010 -3.0 -29.9 23.9
Smith et al. 2000 105.2 70.5 139.9
Body Fat: Isocaloric Carb vs. Fat


Weighted Mean Difference in Body Fat (g/d)

Pooled weighted mean difference

P < 0.0001
Can We Transcend the Diet Wars?

Low Carb  Low Fat
In the case of nutritionism, the widely shared but unexamined assumption is that the key to understanding food is indeed the nutrient. Put another way: Foods are essentially the sum of their nutrient parts.
Diet Quality & Ultra-processed Food

Unprocessed or minimally processed foods include fresh, dried, or frozen vegetables, grains, legumes, fruits, meats, fish, eggs, and milk. They are the basis of healthy dishes and meals.

Ultra-processed foods include fast food, sugary drinks, snacks, chips, candies, cookies, sweetened milk products, sweetened cereals, and sauce and dressings. They are nutritionally poor.
Ultra-processed vs Unprocessed Diets

The meals had similar amounts of: Calories, Carbs, Fat, Protein, Sugar, Sodium, Fiber

20 Adults were instructed to eat as much or as little as desired

Primary Outcome: Energy Intake Differences

Ultra-processed Diets Cause Increased Intake

More Carbs & Fat with Ultra-processed Diets

Larger Meals with Ultra-processed Diets

No Differences in Self-Reported Appetite

No Differences in Pleasantness or Familiarity

Faster Eating Rate for Ultra-processed Meals

Ultra-processed Diets Cause Weight Gain

Ultra-processed Diets Cause Fat Gain

Substantial Individual Variability

Mechanisms?
<table>
<thead>
<tr>
<th>Intramural NIH</th>
<th>Intramural NIDDK</th>
<th>Extramural Collaborators</th>
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<tbody>
<tr>
<td>Amber Courville (CC)</td>
<td>Alexis Ayuketah</td>
<td>Ciaran Forde (Singapore)</td>
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<tr>
<td>Paule Joseph (NINR)</td>
<td>Robert Brychta</td>
<td>Christopher Gardner (Stanford)</td>
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<td>Merel Kozlosky (CC)</td>
<td>Thomas Bemis</td>
<td>Rudy Leibel (Columbia)</td>
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<td>Klaudia Raisinger (CC)</td>
<td>Hongyi Cai</td>
<td>Laurel Mayer (Columbia)</td>
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<td>Shanna Yang (CC)</td>
<td>Thomas Cassimatis</td>
<td>Eric Ravussin (PBRC)</td>
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<td>Dhruva Chandramohan</td>
<td>Jennifer Rood (PBRC)</td>
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<td>Kong Chen</td>
<td>Michael Rosenbaum (Columbia)</td>
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<td>Stephanie Chung</td>
<td>Steven R. Smith (TRI)</td>
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<td>Jon Moon (MEI)</td>
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<td>B. Tim Walsh (Columbia)</td>
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<td>Megan Zhou</td>
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**Special Thanks**

Nursing Staff at the NIH MCRU
Metabolic Kitchen Staff
Volunteer Study Subjects
Nutrition Science Initiative