

Metabolic Flexibility, Energy Availability, and Substrate Utilisation: Extending the EPK Framework Beyond Static Calorie Models

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Abstract

This revision distinguishes energy balance, substrate oxidation, mitochondrial function and body-fat storage. Controlled human feeding supports separating fat oxidation from net fat loss, while tissue and cellular experiments show that the consequences of fuel use depend on context. Recent evidence on adipocyte dysfunction, fatty-acid composition, cortisol metabolism and PUFA is integrated without assuming that all fat oxidation is harmful or that glucose oxidation is sufficient for health. The EPK dietary pattern is a hypothesis to evaluate under specified energy, protein and food-quality conditions. No clinical benefit of PUFA restriction, DCA or nutrient substitutes for DCA is established.

Scope and evidence selection

This is a targeted narrative synthesis and hypothesis paper, updated through 2 October 2026. Sources were selected from the existing EPK evidence library, primary publications and the recent companion reviews. Selection was question-led and not systematic; no pooled effect, formal risk-of-bias score or new participant dataset is reported. Bibliographic records and available abstracts/full texts were used. Abstract-only access limits appraisal of allocation, missing data, confounding and adverse events. Supporting, contrary and null findings are retained.

1. Supply, utilisation and net balance

EPK is defined as mean dietary energy intake in kcal/day divided by body mass in kg. It is an intake-to-total-mass ratio, not a direct measure of energy balance, ATP production or nutritional sufficiency. Sports energy availability instead subtracts exercise expenditure from intake and divides by fat-free mass. Those quantities must be recorded separately; sports thresholds cannot be transferred numerically to EPK. [1]

Dietary intake determines incoming substrate, but does not specify its subsequent oxidation, storage or conversion. A post-meal rise in storage is not permanent tissue gain; mobilisation and oxidation later in the day also matter. A person's respiratory exchange ratio reflects substrate use under the measurement conditions, not a standalone verdict on metabolic health.

In Horton et al.'s overfeeding experiment, carbohydrate and fat excess produced different oxidation and storage responses. In Hall et al.'s controlled restriction trial, carbohydrate restriction raised fat oxidation while fat restriction produced greater calculated body-fat loss during the short observation period.

These experiments distinguish fuel selection from net balance; they do not establish long-term superiority for every population. [2] [3]

2. What counts as low fat?

For EPK research, 20% of dietary energy or less can be a prespecified low-fat category. It is not an established biological threshold. Trials labelled low fat must be described by both prescribed and achieved intake. Carbohydrate quality, fibre, energy density, protein and total intake can differ alongside fat percentage.

Hall et al.'s two-week inpatient comparison found lower spontaneous intake on a plant-based low-fat diet than an animal-based ketogenic diet. Several dietary characteristics differed, and the short crossover period limits longer-term inference. A lower spontaneous intake could benefit a weight-loss outcome while undermining a goal of replenishing energy. [4]

A mouse study comparing carbohydrate sources within low-fat diets found adverse metabolic and inflammatory effects after replacing sucrose with starch in that experimental formulation. This narrow result is not evidence that sugar is universally protective, but reinforces that fat percentage alone does not describe the intervention. [5]

3. Mitochondria, fuel switching and tissue function

Experimental work on incomplete fatty-acid oxidation, cardiac pyruvate handling and genetically excessive cardiac fat oxidation identifies distinct mechanisms of dysfunction. These studies do not show that normal overnight fat use is harmful or that increasing dietary carbohydrate repairs every mitochondrial defect. [6] [7] [8]

Human studies further separate the endpoints. A restriction trial increased muscle mitochondrial DNA content without corresponding changes in key enzyme activities; another comparison found similar insulin-sensitivity improvement despite different mitochondrial adaptations after weight loss or exercise. [9] [10]

Familial partial lipodystrophy research associates loss of functional adipose tissue with metabolic disturbance. It illustrates why less fat tissue is not always better, while its rare genetic context prevents extrapolation to ordinary dieting. Mitochondrial disease can also coexist with hypermetabolism, so higher energy expenditure is not synonymous with healthier energy use. [11] [12]

4. PUFA: exposure, essentiality and location

Rotman et al. studied arachidonic-acid exposure in cultured mammalian cells and found inhibition of protein synthesis. This does not provide a dietary dose-response relationship or a safe intake ceiling. Engineered-cell membrane research also distinguishes fatty-acid species rather than supporting a blanket PUFA category. [13] [14]

In the human LIPOGAIN overfeeding trial, saturated fat produced more liver and visceral-fat accumulation than n-6 PUFA despite similar weight gain. This challenges the proposition that all PUFA preferentially drives harmful ectopic storage. It does not establish lifelong safety at any dose or a mechanism that always directs PUFA away from organs. [15]

An optional PUFA target is therefore a user preference or research variable, not a validated protection threshold. Essential fatty acids must remain adequate. Nutrient databases estimate intake; adipose

composition reflects longer-term exposure, turnover and mobilisation. A rising percentage of one fatty acid during mass loss need not mean its absolute mass increased. [16]

5. Cortisol and intervention claims

Dietary macronutrients can change cortisol regeneration and clearance independently of weight change, without raising measured systemic cortisol. This requires compartment-specific interpretation rather than labelling a food uniformly stressful. [17]

The DCA obesity thesis discussed in the companion review was not available for primary appraisal. DCA is not interchangeable with thiamine, magnesium or niacinamide simply because these relate to pyruvate metabolism. No supplement protocol or cancer-treatment conclusion follows from this paper. [18]

6. Testing the metabolic hypothesis

First choose the estimand: the effect of a full EPK package, the energy-target method, or fat/carbohydrate substitution at matched energy and protein. These require different comparators. Document actual intake and changes in activity; equal prescribed calories do not guarantee equal achieved balance.

Because the ratio is determined entirely by intake and mass, it cannot contain information absent from those inputs. Its usefulness is a question of practical summarisation and predictive performance. Compare a prespecified EPK model with flexible models of intake, mass, fat-free mass and activity, including nonlinear terms where justified. Use the same held-out validation procedure, report calibration and uncertainty, and prefer the simpler model if performance is similar. A favourable comparison with a deliberately weak linear model would not establish a new biological quantity.

Measure fasting-to-fed substrate switching under standardised prior diet and exercise. Use indirect calorimetry for whole-body oxidation, and distinguish it from tissue respiration, glycaemic control and net fat change. A mechanistic subgroup could use tracers or imaging if feasible; wearable calories cannot act as the reference standard for their own validation.

An improved respiratory measure without better function would not establish clinical value. Improved glucose handling without greater mitochondrial capacity would favour a narrower mechanism. Fat loss accompanied by impaired recovery should not be treated as unconditional success.

Conclusion

EPK's substrate hypothesis is most useful when it makes separate predictions about intake, fuel switching, tissue storage and function. The evidence supports that separation. It does not support universal avoidance of fat oxidation or a clinically established PUFA ceiling.

Version and disclosure

Version 1.2 integrates controlled feeding, adipose function and recent PUFA findings; corrects fuel-oxidation/storage conflation; specifies low-fat exposure and essential-fat safeguards; and removes unsupported drug-to-supplement equivalence. This version supersedes v1.1.1 for the current text; the earlier PDF and DOI remain an archive of that release. Reference numbering has been rebuilt for this version and must not be transferred from earlier editions.

The author develops EPK and has an intellectual and potential commercial interest in its evaluation. AI-assisted editorial drafting and source checking were used. This independent working paper has not undergone external peer review. No new human intervention or participant analysis is reported. Copyright 2026 Billy Craig. Author-owned text is licensed CC BY-ND 4.0; third-party material retains its own rights.

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Version history

v1.2 - 2 October 2026: scientific and editorial revision, refreshed reference mapping and integrated recent evidence. Unverified MSc quantitative claims are excluded from the evidential basis.

v1.1.1 - 11 September 2026: earlier licensing release. Archived DOI: 10.5281/zenodo.22710004. Earlier versions remain available through Zenodo.

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