

Energy Availability, Metabolic Flexibility, and Cognitive Aging: Extending the EPK Framework Toward Neuroenergetic Health

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Status: conceptual/hypothesis-generating working paper. Not peer reviewed. This revision adds primary-study appraisal and prospective tests; it reports no new participant data.

Abstract

Aging and neurodegenerative disease are associated with impairments in cerebral glucose metabolism, mitochondrial function and metabolic flexibility. This paper explores whether chronic low-energy physiology and altered substrate competition may contribute to reduced neuroenergetic resilience. It does not claim that dietary fat causes dementia or that carbohydrate prevents Alzheimer's disease.^{1,2,3,4,5,6,7} This revision separates dietary intake from cellular utilisation and proposes prospective comparison of EPK with its component measurements; the added mechanistic evidence does not validate EPK.

The Energetic Brain

The brain consumes a large share of resting energy and normally relies heavily on glucose. Cerebral glucose utilisation is especially high during childhood, a period of rapid development, synaptic activity and behavioural vitality. In contrast, aging and Alzheimer's disease are frequently associated with reduced glucose uptake in vulnerable brain regions. This contrast motivates investigation of energetic throughput across the lifespan without implying that youthful metabolism can simply be recreated by diet.^{4,5,6,7,8,9}

Aging and Metabolic Flexibility

Aging is associated with impaired insulin sensitivity, reduced mitochondrial function, lower spontaneous movement and poorer substrate flexibility. These changes may be consequences of multiple interacting processes rather than age alone. Within EPK, chronic low energy, reduced movement and poor recovery are proposed as potential contributors to a progressively lower-throughput state.^{10,11}

Randle Cycle and Substrate Competition

The glucose-fatty-acid cycle describes reciprocal competition between fatty-acid and glucose oxidation. High fatty-acid availability can suppress glucose oxidation. This is normal physiology, but chronic inflexibility may become relevant when high fatty-acid exposure, low movement and impaired glucose handling coexist. The EPK hypothesis is that adequate carbohydrate availability and restored movement may support glucose oxidation while stored fat remains available during lower-demand states.^{1,2,3}

PUFA, Lipid Peroxidation and Neuroenergetic Stress

Highly unsaturated lipids are vulnerable to peroxidation, and oxidised lipid products are observed in aging and neurodegenerative disease. These findings justify mechanistic study but do not establish that dietary PUFA is a singular cause of dementia. EPK treats lipid composition as one possible modifier within a broader system of oxidative stress, mitochondrial function, energy availability and movement.^{12,13,14,15,16,4,5}

Sleep and cellular aging as separate hypotheses

Sarnataro et al. investigated mitochondrial regulation of sleep pressure in fruit flies [R1]. Yamauchi et al. examined fatty-acid oxidation and cellular senescence in experimental systems [R2]. Neither study tested EPK or demonstrated prevention of human cognitive decline. They suggest separate candidate mechanisms that should not be collapsed into a single account of brain aging.

Gupta et al. provide a membrane-specific reason to distinguish individual fatty acids and tissue contexts [R3]. Their engineered-cell results do not establish that dietary PUFA causes dementia. Similarly, evidence of senescence in fibroblasts cannot be assumed to describe the physiology of mature neurons.

Human evidence from the PubMed search

Twenty women completed three-day conditions. Diet-induced low energy availability did not alter the measured cognitive outcomes; exercise-induced low availability affected mental-rotation accuracy relative to balanced intake, while other outcomes were unchanged. This limits a general claim that short-term low energy availability broadly impairs cognition. [H1]

These studies test energy restriction or sports energy availability, not EPK as an intake-to-total-mass ratio. Their populations and intervention durations bound interpretation; none validates an EPK threshold. The human literature requires the framework to allow beneficial, adverse and null responses in different contexts.

A longitudinal cognitive study

Does EPK predict functional outcomes beyond total energy intake, body composition, carbohydrate availability and activity, and could fuel switching or mitochondrial function explain any association?

For prospective testing, EPK is defined here as mean dietary energy intake in kcal per day divided by body mass in kg, expressed as kcal/kg/day. This intake ratio is not the sports energy-availability measure, which subtracts exercise energy expenditure from intake and divides by fat-free mass. Exercise expenditure, fat-free mass, carbohydrate intake and weight trajectory must therefore be recorded separately. No diagnostic EPK threshold is established by this revision.

Prespecify a validated cognitive outcome and follow participants long enough to distinguish persistent change from day-to-day variation. Repeated testing needs alternate forms or other safeguards against practice effects. Record education, baseline cognition, mood, sleep, vascular risk, medication, physical activity, diet and body composition. Illness can reduce intake before cognitive decline becomes apparent, making reverse causation a central concern.

EPK is calculated from intake and mass and therefore contains no information absent from those inputs. Its value must be judged as a useful summary, not an independent biological variable. Compare a preregistered EPK model with a flexible model of energy intake and mass, including relevant nonlinear terms and interactions, under the same validation procedure. Adding the ratio to a simple linear baseline would not by itself establish unique physiological information. Report out-of-sample prediction error, calibration and uncertainty; favour the simpler model if performance is comparable.

Whole-body fuel switching can be assessed as an accompanying phenotype, but cannot establish brain glucose uptake or neuronal mitochondrial function. A brain-specific imaging or metabolic substudy would require an

explicit protocol and its own interpretation. Prospective associations are hypothesis tests; demonstrating prevention would require an intervention study with cognitive outcomes.

Conclusion

Cognitive aging is multifactorial. The EPK contribution is a testable systems hypothesis: preserving energetic sufficiency, movement, glucose-handling capacity and metabolic flexibility may be relevant to long-term neuroenergetic resilience.^{1,2,3,4,5,6,7}

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Primary studies added in version 1.1

[R1] Sarnataro R, Velasco CD, Monaco N, Kempf A, Miesenböck G. Mitochondrial origins of the pressure to sleep. *Nature*. 2025;645:722–728. <https://doi.org/10.1038/s41586-025-09261-y>

[R2] Yamauchi S, et al. Mitochondrial fatty acid oxidation drives senescence. *Sci Adv*. 2024;10:eado5887. <https://doi.org/10.1126/sciadv.ado5887>

[R3] Gupta P, et al. Kingdom-specific lipid unsaturation calibrates sequence evolution in membrane arm subunits of eukaryotic respiratory complexes. *Nat Commun*. 2025;16:2044. <https://doi.org/10.1038/s41467-025-57295-7>

Human studies added in version 1.1

[H1] Martin D, et al. The effects of short-term low energy availability, achieved through diet or exercise, on cognitive function in oral contraceptive users and eumenorrheic women. *Appl Physiol Nutr Metab*. 2021;46:781–789. doi:10.1139/apnm-2020-0474. <https://pubmed.ncbi.nlm.nih.gov/33400618/>

Publication Note

This manuscript is part of the EPK (Energy Per Kilogram) paper series developed by Billy Craig, MSc. The paper should be cited as a working/preprint paper until peer-reviewed publication. EPK-specific propositions are presented as hypotheses where they extend beyond the cited evidence.

Revision record

Version 1.1 adds the mechanistic discussion and prospective study design above. The original numbered bibliography remains distinct from the new R-prefixed mechanistic and H-prefixed human-study citations. Studies discovered through haidut.me are cited to their original research publications; the blog commentary is not treated as primary evidence.

Original v1.0: <https://doi.org/10.5281/zenodo.22673295>. Version 1.1.1 (11 September 2026) changes licensing only; scientific content is unchanged from v1.1. CC BY-ND 4.0 applies to author-owned text; third-party material is excluded. No new DOI is assigned in this file.