Review

What Are Humans Designed to Eat? An IOM Systems Medicine Framework for Dietary Compatibility, Nutrient Density, and Toxicological Burden

Richard Z. Cheng *

Posted Date: 9 May 2026

doi: 10.20944/preprints202605.0616.v1

Keywords: IOM Systems Medicine; systems nutrition; human nutrition; dietary patterns; metabolic flexibility; energetic resilience; mitochondrial energetics; metabolic health; chronic disease; nutritional systems biology; ketogenic diet; low-carbohydrate diet; fasting metabolism; evolutionary nutrition; nutrient density; toxicological burden; orthomolecular medicine

 doi:10.20944/preprints202605.0616.v1

Review

What Are Humans Designed to Eat? An IOM Systems Medicine Framework for Dietary Compatibility, Nutrient Density, and Toxicological Burden

Richard Z. Cheng [1,2]

[1] Cheng Integrative Health Center, Columbia, SC, USA

[2] Cheng Health Consulting, Ltd., Shanghai, China

* Correspondence: richzc@gmail.com

Abstract

Modern dietary debates remain highly polarized among competing nutritional paradigms, including low-fat, Mediterranean, plant-based, vegan, low-carbohydrate, ketogenic, and animal-based dietary models. Despite decades of nutritional guidelines and extensive epidemiological research, chronic diseases—including obesity, type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease (ASCVD), autoimmune disorders, cancer, and neurodegenerative diseases—continue to rise globally. These trends raise an important question: are prevailing nutritional frameworks adequately aligned with human physiology, metabolic biology, and long-term systems resilience? This paper proposes an Integrative Orthomolecular Medicine (IOM) Systems Medicine framework for evaluating human diets based not solely on caloric intake or macronutrient composition, but on broader biological principles including metabolic compatibility, metabolic flexibility, nutrient density and bioavailability, mitochondrial energetics, inflammatory regulation, biological barrier integrity, oxidative-reduction balance, and cumulative toxicological burden. We first examine evolutionary and physiological foundations of human nutrition, emphasizing omnivorous adaptation, fuel-switching physiology, fasting metabolism, and the evolutionary importance of energetic resilience during periods of food scarcity, migration, hunting, and prolonged physical exertion. Particular attention is given to the human capacity for metabolic flexibility—the ability to transition between glucose utilization, fatty acid oxidation, and ketone metabolism according to energetic demands and nutrient availability. We propose the Energetic Resilience Principle, which suggests that nutritional systems should be evaluated not solely according to glycemic control, but also according to their effects on mitochondrial energetics, fuel adaptability, endurance capacity, fasting tolerance, and long-term physiological resilience. Particular attention is also given to the absence of a clearly established minimum dietary carbohydrate requirement in the presence of adequate protein and fat intake. We then compare major dietary models—including the Standard American Diet (SAD), Mediterranean, plant-based and vegan, low-carbohydrate, ketogenic, and carnivore/elimination-based approaches—across multiple domains relevant to metabolic health and systems biology. Particular attention is given to the potential consequences of chronic dependence on highly refined, continuously fed, hyperinsulinemic metabolic states, including impaired metabolic flexibility, mitochondrial stress, oxidative imbalance, and reduced physiological adaptability. Special attention is given to the nutritional and toxicological characteristics of both plant- and animal-derived foods. While plant foods provide fiber, phytonutrients, vitamins, and numerous bioactive compounds, they may also contain naturally occurring defense compounds such as lectins, oxalates, phytates, alkaloids, and gluten-related proteins, in addition to agricultural contaminants including pesticides, herbicides, and microplastics. Conversely, animal-derived foods may bioaccumulate persistent fat-soluble pollutants and environmental contaminants. The paper further proposes that plant-heavy and animal-heavy dietary systems may differ in dominant toxicological exposure profiles, including relative tendencies toward water-soluble agricultural contaminants and plant defense compounds versus fat-soluble bioaccumulated environmental pollutants. Accordingly, this paper proposes that no modern dietary

 doi:10.20944/preprints202605.0616.v1

system is entirely toxin-free, and that dietary strategies should instead be evaluated according to cumulative toxicological burden, nutrient sufficiency, metabolic effects, mitochondrial support, and biological compatibility. Finally, this paper proposes a hierarchical IOM Systems Nutrition framework emphasizing:

- low glycemic burden,
- low ultra-processing burden,
- low cumulative toxicological burden from both natural and industrial exposures,
- nutrient sufficiency,
- metabolic flexibility,
- mitochondrial support,
- preservation of energetic resilience,
- and long-term physiological adaptability.

Within this framework, nutrition is viewed not merely as a source of calories or macronutrients, but as a systems-level regulator of mitochondrial energetics, metabolic resilience, endocrine signaling, inflammatory regulation, biological integrity, adaptive stress responses, and long-term physiological resilience. The framework proposed is intended as a comparative systems-based model for evaluating dietary compatibility with human physiology and adaptive metabolism, rather than a universal prescription for any single dietary pattern.

Keywords: IOM Systems Medicine; systems nutrition; human nutrition; dietary patterns; metabolic flexibility; energetic resilience; mitochondrial energetics; metabolic health; chronic disease; nutritional systems biology; ketogenic diet; low-carbohydrate diet; fasting metabolism; evolutionary nutrition; nutrient density; toxicological burden; orthomolecular medicine

1. Introduction

Modern nutrition science remains increasingly fragmented among competing dietary paradigms, including low-fat, Mediterranean, vegetarian, vegan, low-carbohydrate, ketogenic, and animal-based dietary approaches. Despite decades of evolving nutritional guidelines and extensive epidemiological research, the global prevalence of chronic metabolic disease continues to rise. According to the World Health Organization (WHO), noncommunicable diseases (NCDs) now account for approximately 74% of global deaths, with cardiovascular disease, cancer, diabetes, and chronic respiratory diseases representing the major contributors[1]. Simultaneously, obesity and type 2 diabetes mellitus (T2DM) have increased dramatically worldwide over recent decades[2,3]. These trends raise important questions regarding whether prevailing nutritional frameworks are adequately aligned with human physiology, metabolic biology, energetic resilience, and long-term systems health.

Increasing evidence suggests that many chronic illnesses—including obesity, insulin resistance, T2DM, atherosclerotic cardiovascular disease (ASCVD), nonalcoholic fatty liver disease (NAFLD), autoimmune disorders, neurodegenerative diseases, and cancer—are not isolated organ-specific conditions, but rather complex systems-level disorders involving dynamic interactions among metabolism, mitochondrial energetics, endocrine signaling, immune regulation, oxidative-reduction balance, environmental toxicology, gut and biological barrier integrity, circadian biology, and nutritional status[4–10]. Within this framework, chronic disease may emerge when cumulative physiological burden exceeds the body's adaptive and restorative capacity.

Mitochondrial dysfunction, impaired metabolic flexibility, loss of energetic adaptability, and chronic hyperinsulinemia have increasingly emerged as central features linking many chronic diseases previously viewed as distinct clinical entities[11–14]. Hyperglycemia, chronic inflammation, oxidative stress, circadian disruption, micronutrient insufficiency, sedentary behavior, and environmental toxicant exposure may collectively contribute to progressive systems dysregulation

 doi:10.20944/preprints202605.0616.v1

and declining biological resilience[7,15–21]. These observations suggest that nutrition exerts biological effects extending far beyond simple caloric provision or macronutrient partitioning alone.

Historically, nutrition science has often emphasized relatively reductionist endpoints such as caloric balance, isolated nutrient restriction, serum lipid measurements, and short-term epidemiological associations. While these approaches have generated important mechanistic insights, they may insufficiently address broader biological questions central to long-term health and disease prevention. These include determining which dietary patterns are most biologically compatible with human physiology, how diets should be evaluated beyond caloric quantity and macronutrient ratios, and what roles nutrient density, nutrient bioavailability, food processing, mitochondrial support, metabolic flexibility, and toxicological burden play in chronic disease development and physiological resilience.

At the same time, increasing concerns have emerged regarding modern industrialized food systems. Ultra-processed foods (UPFs), characterized by industrial formulations containing refined carbohydrates, industrial seed oils, additives, emulsifiers, artificial flavoring systems, and engineered hyperpalatable ingredients, have been associated with obesity, insulin resistance, cardiovascular disease, metabolic dysfunction, and increased all-cause mortality[22–25]. In parallel, modern agricultural and environmental practices have increased human exposure to pesticides, herbicides, endocrine-disrupting compounds, heavy metals, microplastics, and other environmental contaminants throughout the food chain[26–29]. These exposures may interact with metabolic dysfunction, oxidative stress, mitochondrial injury, inflammatory signaling, and impaired biological barrier integrity.

Growing scientific and public interest has also emerged regarding low-carbohydrate and ketogenic dietary approaches for metabolic disease management. Clinical trials and mechanistic studies suggest that carbohydrate restriction and nutritional ketosis may improve glycemic control, insulin sensitivity, body composition, mitochondrial energetics, inflammatory regulation, and metabolic flexibility in selected populations[30–34]. From an evolutionary and energetic perspective, the ability to efficiently transition between glucose and fatty acid utilization during periods of intermittent food scarcity may represent an important component of human physiological resilience. Impaired metabolic flexibility and chronic dependence on continuous glucose availability may therefore contribute to reduced energetic adaptability and increased vulnerability to metabolic dysfunction.

Conversely, plant-based dietary patterns continue to receive considerable attention because of their associations with increased intake of fiber, phytonutrients, and antioxidant compounds[35–38]. Nevertheless, important questions remain regarding amino acid quality, micronutrient sufficiency, mineral bioavailability, glycemic burden, ultra-processing of commercial plant-based substitute products, and the biological effects of naturally occurring plant defense compounds, including lectins, oxalates, phytates, alkaloids, and gluten-related proteins[35–40]. Importantly, neither plant-based nor animal-based food systems appear entirely free of nutritional limitations or toxicological tradeoffs. Importantly, different dietary systems may shift toxicological exposure profiles rather than eliminate toxic burden altogether, including differing tendencies toward water-soluble agricultural contaminants versus fat-soluble bioaccumulated pollutants.

These ongoing controversies suggest the need for a broader systems-level nutritional framework capable of integrating metabolic resilience, mitochondrial energetics, nutrient density, food processing, toxicological burden, and long-term physiological adaptability. Rather than evaluating diets primarily through ideological or macronutrient-centered perspectives, nutrition may need to be reframed within the broader context of systems biology and human physiological compatibility.

This paper therefore proposes an Integrative Orthomolecular Medicine (IOM) Systems Medicine framework for human nutrition emphasizing biological compatibility, metabolic flexibility, nutrient density and bioavailability, mitochondrial support, inflammatory regulation, biological barrier integrity, reduction of toxicological burden, oxidative-reduction balance, and restoration of systems-level resilience. Within this paradigm, nutrition is viewed not merely as a source of calories, but as a

 doi:10.20944/preprints202605.0616.v1

foundational biological signaling system influencing mitochondrial bioenergetics, endocrine networks, immune regulation, vascular integrity, microbiome ecology, cellular repair mechanisms, and long-term healthspan trajectories. Dietary patterns should therefore be evaluated according to their integrated effects on metabolism, nutrient sufficiency, inflammatory burden, toxicological exposure, mitochondrial resilience, energetic adaptability, and physiological resilience rather than according to rigid dietary ideology alone.

2. Evolutionary and Physiological Foundations of Human Nutrition

2.1. Humans as Metabolically Flexible Omnivores

Human physiology evolved under highly variable environmental and nutritional conditions characterized by intermittent food availability, seasonal fluctuations, geographic diversity, and shifting macronutrient exposure. Throughout much of human evolutionary history, food scarcity rather than chronic caloric excess represented the dominant metabolic challenge. As a result, humans evolved remarkable metabolic flexibility—the ability to transition among multiple energy substrates according to nutrient availability, energetic demands, and physiological conditions[41–44].

Humans are capable of utilizing carbohydrates, fatty acids, ketone bodies, and amino acids as metabolic fuels through tightly regulated endocrine and mitochondrial pathways. Under carbohydrate-fed conditions, glucose serves as a major energy substrate, particularly for glycolysis-dependent tissues. During fasting, prolonged exercise, caloric restriction, or carbohydrate restriction, humans can transition toward increased fatty acid oxidation and ketogenesis, producing ketone bodies—including beta-hydroxybutyrate and acetoacetate—as alternative fuels for the brain, skeletal muscle, and other tissues[13,45–47].

This capacity for metabolic switching appears to represent a fundamental evolutionary adaptation that supported survival during fluctuating food availability, prolonged physical exertion, migratory activity, and fasting conditions. Metabolic flexibility is increasingly recognized as an important marker of metabolic health, whereas metabolic inflexibility has been associated with obesity, insulin resistance, T2DM, NAFLD, mitochondrial dysfunction, and chronic inflammatory states[14,48].

Unlike obligate herbivores or obligate carnivores, humans demonstrate physiological characteristics consistent with omnivorous adaptation. Human dietary evolution likely involved substantial variability depending on geography, climate, migration patterns, seasonality, and food availability[49–53]. Anthropological and isotopic evidence suggests that ancestral human diets ranged from relatively plant-dominant to highly animal-based dietary patterns depending on ecological conditions and environmental constraints[38,54].

Several physiological observations support human omnivorous flexibility, including relatively short gastrointestinal tract length compared with herbivores, gastric acid production capable of handling animal proteins, the capacity for ketogenesis during carbohydrate scarcity, the ability to digest both plant and animal foods, and substantial adaptability in fuel utilization.

Importantly, no clearly established minimum dietary carbohydrate requirement exists in humans when adequate protein and fat intake are present. Glucose requirements for obligate glycolytic tissues can be met through endogenous gluconeogenesis, while ketone bodies may partially replace glucose utilization during fasting or carbohydrate restriction[31,33,55].

This evolutionary perspective does not imply that any single universal “ancestral diet” existed. Rather, it suggests that human physiology evolved to tolerate a broad range of nutritional environments while maintaining metabolic adaptability and survival capacity. However, modern industrial dietary environments differ profoundly from ancestral nutritional conditions in several important respects, including continuous caloric abundance, chronic hyperinsulinemic feeding patterns, ultra-processed foods, refined sugars and starches, industrial seed oils, altered omega-6 to omega-3 ratios, reduced micronutrient density, reduced dietary diversity, sedentary lifestyles, circadian disruption, and increased environmental toxicological exposure[22,23,26,28,56].

 doi:10.20944/preprints202605.0616.v1

The rapid global rise in obesity, metabolic syndrome, T2DM, ASCVD, and NAFLD over recent decades has paralleled dramatic increases in ultra-processed food consumption and industrialized dietary patterns[3,57–59]. Increasing evidence suggests that chronic metabolic disease may result not simply from excess caloric intake, but from broader systems-level dysregulation involving mitochondrial dysfunction, chronic hyperinsulinemia, inflammation, oxidative stress, circadian disruption, microbiome alterations, endocrine dysregulation, and cumulative toxicological burden[4,9–11,18,21].

Within this context, metabolic flexibility and energetic resilience may represent central features of human physiological adaptability. Dietary patterns that impair the ability to transition efficiently between glucose and fat metabolism may contribute to progressive metabolic dysfunction. Conversely, dietary strategies that restore metabolic adaptability—including fasting, carbohydrate restriction, reduction of ultra-processed foods, and improved nutrient density—may improve systems-level health in selected populations[58,60–62].

From an IOM Systems Medicine perspective, optimal human nutrition should therefore be evaluated not solely according to macronutrient composition, but according to broader biological compatibility with human physiology, including metabolic flexibility, mitochondrial support, inflammatory regulation, nutrient density and bioavailability, toxicological burden, endocrine balance, biological barrier integrity, and long-term systems resilience.

2.2. Essential Nutrients and Human Biological Requirements

Essential nutrients required for human survival include essential amino acids, essential fatty acids, vitamins, minerals, trace elements, and water. These nutrients must be obtained directly or indirectly through dietary intake because humans cannot synthesize them in sufficient quantities endogenously[21,55]. Nutritional adequacy therefore depends not merely on caloric intake, but on the provision of biologically available nutrients necessary for cellular structure, mitochondrial energy production, enzymatic reactions, endocrine regulation, immune function, tissue repair, and maintenance of systemic homeostasis.

Importantly, no clearly established biochemical requirement exists for refined sugars or ultra-processed carbohydrates in human physiology. Furthermore, no minimum dietary carbohydrate requirement has been established in the presence of adequate protein and fat intake capable of supporting endogenous glucose production and ketogenesis[31,33].

This observation should not be interpreted to mean that carbohydrates are inherently harmful or universally unnecessary. Rather, it reflects the remarkable metabolic adaptability of human physiology.

Humans possess highly conserved physiological mechanisms capable of maintaining glucose homeostasis during periods of reduced carbohydrate availability. Through hepatic and renal gluconeogenesis, glucose can be synthesized from non-carbohydrate substrates including amino acids, lactate, glycerol, and pyruvate[45,63,64]. In parallel, ketogenesis allows the liver to produce ketone bodies—including beta-hydroxybutyrate and acetoacetate—from fatty acids during fasting, starvation, prolonged exercise, or carbohydrate restriction[13,46,47].

These adaptations appear to represent ancient survival mechanisms that enabled humans to tolerate fluctuating nutritional environments throughout evolution. During prolonged fasting or nutritional ketosis, ketone bodies may provide a substantial proportion of cerebral energy requirements, thereby reducing dependence on exogenous carbohydrate intake[46,65,66].

Classic metabolic studies by Cahill, Owen, and colleagues demonstrated that during prolonged fasting, ketone bodies become major cerebral fuels while glucose requirements decline substantially[46,65]. Veech and others later proposed that ketone metabolism may provide unique energetic and signaling advantages under selected physiological and pathological conditions, including improved mitochondrial energetics, altered redox regulation, and reduced oxidative stress[13,67].

 doi:10.20944/preprints202605.0616.v1

Increasing evidence suggests that metabolic flexibility—the ability to efficiently transition between glucose and fat oxidation—represents an important hallmark of metabolic health[14,48]. Conversely, impaired metabolic flexibility has been associated with obesity, insulin resistance, T2DM, NAFLD, mitochondrial dysfunction, and chronic inflammation[68].

Importantly, these observations should not be interpreted as support for a single universal dietary prescription. Human carbohydrate tolerance likely varies considerably according to insulin sensitivity, metabolic status, physical activity, mitochondrial function, age, body composition, circadian biology, genetic predisposition, and disease state.

For metabolically healthy and physically active individuals, whole-food carbohydrate consumption may be well tolerated. However, in individuals with insulin resistance, obesity, metabolic syndrome, T2DM, or impaired mitochondrial function, excessive intake of refined carbohydrates and ultra-processed foods may contribute to chronic hyperinsulinemia, metabolic inflexibility, oxidative stress, and progressive systems dysfunction[22,23,58].

Importantly, modern carbohydrate exposure differs substantially from that encountered during most of human evolutionary history. Contemporary industrialized diets often involve highly refined starches, concentrated sugars, ultra-processed foods, engineered hyperpalatable products, continuous snacking behavior, and chronically elevated insulin exposure[44,59,61,69]. Such dietary environments may place substantial stress on metabolic regulatory systems that evolved under conditions of intermittent food availability and greater nutritional variability.

From an IOM Systems Medicine perspective, dietary carbohydrates should therefore be evaluated not solely according to quantity, but according to glycemic burden, degree of processing, nutrient density, metabolic context, mitochondrial effects, inflammatory impact, endocrine responses, and overall biological compatibility.

This framework emphasizes that optimal nutrition should support metabolic flexibility, energetic adaptability, nutrient sufficiency, mitochondrial resilience, and long-term systems stability rather than merely achieving short-term caloric targets.

3. The Energetic Resilience Principle

A central objective of this paper is to broaden modern nutritional discourse beyond a narrow focus on blood glucose regulation alone. Much of contemporary dietary debate has centered on blood sugar, insulin, calorie balance, serum lipids, and body weight. While these parameters remain clinically important, they may insufficiently capture broader dimensions of human physiological function, energetic adaptability, and long-term systems resilience.

Human physiology evolved under environmental conditions fundamentally different from modern industrialized dietary environments. Throughout most of human evolutionary history, survival depended not on continuous carbohydrate availability, but on the ability to maintain physical and cognitive performance during intermittent food scarcity, prolonged physical exertion, migratory activity, hunting, environmental stress, and fluctuating nutrient availability[14,44,45,70,71].

I propose the Energetic Resilience Principle: human metabolic health should be evaluated not only by glucose control, but also by the capacity to maintain stable energy production during fasting, prolonged physical activity, carbohydrate restriction, and other periods of reduced exogenous glucose availability. This includes efficient fuel switching, fat oxidation, ketone utilization, mitochondrial adaptability, and resistance to hypoglycemic energy collapse.

From an evolutionary physiology perspective, this capacity likely represented a survival advantage during periods of food scarcity, prolonged hunting, migration, seasonal variation, or intermittent access to carbohydrate-dense foods.

Accordingly, humans evolved substantial metabolic flexibility, including the capacity to efficiently transition between glucose utilization, fatty acid oxidation, and ketone metabolism depending on energetic demands and nutrient availability[13,46,66,72,73]. From a physiological

 doi:10.20944/preprints202605.0616.v1

perspective, this fuel-switching capacity appears to represent a major evolutionary adaptation supporting survival during fasting and prolonged exertion lipolysis.

During periods of reduced carbohydrate availability, humans are capable of increasing lipolysis, hepatic fatty acid oxidation, ketogenesis, and ketone utilization by the brain, skeletal muscle, and myocardium[46,74–77].

Studies of ketogenic adaptation and ultra-endurance athletes show that humans can substantially increase fat oxidation during prolonged exercise after adaptation to carbohydrate restriction, supporting the concept that metabolic flexibility and fat-based energetics are central features of human physiological resilience[78–80].

Classic metabolic studies by Cahill, Owen, and colleagues demonstrated that prolonged fasting induces major shifts toward ketone utilization, allowing preservation of blood glucose for obligate glycolytic tissues while maintaining cerebral energetics through ketone metabolism[74,75]. Veech and others later proposed that ketone bodies may provide unique mitochondrial and energetic advantages under selected physiological conditions, including altered redox balance, improved aspects of mitochondrial energetic efficiency, reduced reactive oxygen species generation, and enhanced energetic stability[13,74].

From an IOM Systems Medicine perspective, preservation of this metabolic adaptability may represent a foundational feature of physiological resilience, mitochondrial stability, endurance capacity, energetic efficiency, fasting tolerance, and long-term metabolic health. This concept is referred to here as the Energetic Resilience Principle (Figure 1).

This does not imply that carbohydrate intake is unnecessary for all forms of high-intensity performance, but it suggests that long-term health and endurance physiology cannot be adequately understood through a glucose-centered model alone.

The Energetic Resilience Principle proposes that optimal nutrition should not be evaluated solely according to short-term glycemic markers, but also according to its effects on metabolic flexibility, mitochondrial energetics, fuel-switching capacity, sustained energy stability, resilience during fasting or physiological stress, and the ability to maintain functional performance without continuous dependence on frequent carbohydrate intake.

Within this framework, chronic metabolic dysfunction may reflect not merely impaired glucose regulation, but progressive loss of metabolic flexibility and energetic resilience. Individuals with severe insulin resistance, obesity, metabolic syndrome, or T2DM frequently exhibit impaired capacity to transition efficiently between glucose and fat metabolism, a phenomenon increasingly described as metabolic inflexibility[14,70,72,76,77].

Modern industrialized dietary patterns may further exacerbate this problem through chronic hyperinsulinemic feeding, frequent snacking behavior, continuous caloric exposure, ultra-processed carbohydrate consumption, reduced fasting intervals, sedentary lifestyles, and disrupted circadian biology[23,58,61,81]. Emerging evidence also suggests that feeding timing and circadian alignment may substantially influence metabolic flexibility, mitochondrial function, insulin sensitivity, and energetic resilience. Experimental and clinical studies on time-restricted feeding (TRF) indicate that limiting feeding windows and restoring fasting intervals may improve metabolic regulation, circadian synchronization, mitochondrial energetics, and adaptive stress responses independent of caloric restriction alone[82]. These observations further support the concept that human physiology evolved under conditions of intermittent feeding and fluctuating nutrient availability rather than continuous caloric exposure throughout the waking day.

Under such conditions, many individuals may become increasingly reliant on frequent carbohydrate intake to maintain perceived energy stability while simultaneously losing efficient access to endogenous fat stores as metabolic fuel.

From a systems-level perspective, this loss of energetic adaptability may contribute to fatigue, impaired endurance, unstable energy regulation, mitochondrial stress, chronic inflammation, oxidative stress, and progressive metabolic dysfunction.

 doi:10.20944/preprints202605.0616.v1

Importantly, the Energetic Resilience Principle should not be interpreted as support for a single universal dietary prescription or continuous nutritional ketosis in all individuals. Human carbohydrate tolerance likely varies according to metabolic status, physical activity, mitochondrial function, genetics, age, body composition, endocrine regulation, and disease state. Rather, this principle emphasizes preservation of the physiological capacity for flexible fuel utilization as a central component of human health and metabolic resilience.

Within this framework, dietary systems may be evaluated not merely according to caloric quantity or macronutrient ideology, but according to their ability to support stable mitochondrial energetics, efficient fuel adaptability, nutrient sufficiency, inflammatory regulation, physiological resilience, and long-term systems stability.

The Energetic Resilience Principle proposes that human metabolism evolved to maintain adaptive fuel flexibility across changing physiological and environmental conditions, as illustrated in Figure 1.

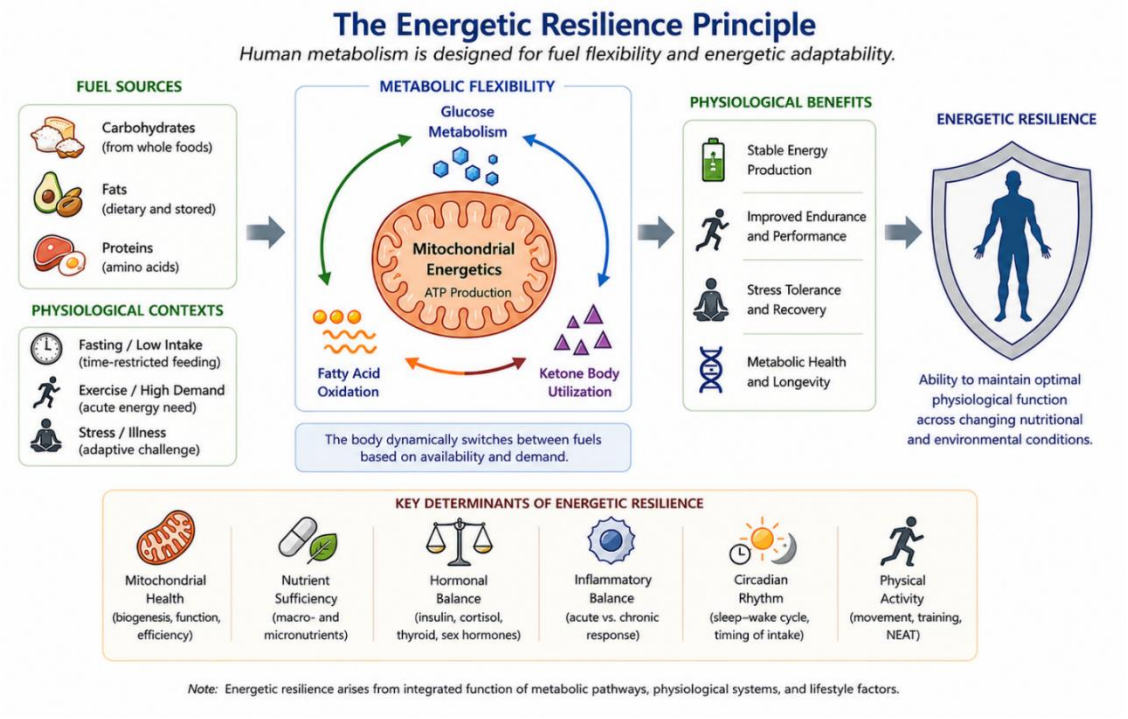

Figure 1. ***The Energetic Resilience Principle.*** Human metabolism is inherently designed for fuel flexibility and energetic adaptability. This figure illustrates the concept of energetic resilience, defined as the capacity to maintain stable physiological function across changing nutritional, environmental, and metabolic conditions through adaptive fuel utilization and resilient mitochondrial energetics. Depending on nutrient availability, fasting status, physical activity, stress exposure, and energetic demand, human metabolism is capable of dynamically shifting among glucose metabolism, fatty acid oxidation, and ketone body utilization. Central to this adaptive process is mitochondrial function, which integrates nutrient sufficiency, hormonal regulation, inflammatory balance, circadian rhythm integrity, and physical activity to maintain efficient ATP production and systems-level homeostasis. Physiological benefits associated with preserved energetic resilience may include stable energy production, enhanced endurance capacity, improved stress tolerance and recovery, metabolic flexibility, and long-term metabolic health. From an IOM Systems Medicine perspective, energetic resilience represents a core systems-level determinant of biological adaptability, mitochondrial function, and long-term physiological resilience.

 doi:10.20944/preprints202605.0616.v1

4. Nutrient Density and Bioavailability

4.1. Nutrient Density Versus Caloric Density

Modern nutritional discourse frequently emphasizes caloric quantity while underemphasizing nutrient density and nutrient bioavailability. Although caloric balance influences body weight regulation, human physiology depends fundamentally on the adequate intake and utilization of essential nutrients required for mitochondrial energy production, enzymatic reactions, immune regulation, tissue repair, endocrine signaling, maintenance of systemic homeostasis, mitochondrial energetics, and long-term physiological resilience.

Importantly, foods differ substantially not only in caloric content, but also in amino acid composition, vitamin content, mineral concentration, mineral absorption, fatty acid composition, digestibility, and biological availability of nutrients. As a result, nutritional adequacy depends not solely on food quantity, but also on the biological accessibility, absorption efficiency, and metabolic utility of nutrients contained within foods[21,83–85].

Historically, nutritional guidelines have often prioritized relatively reductionist targets such as total calories, total fat, saturated fat, or cholesterol while giving comparatively less attention to overall nutrient density, protein quality, and nutrient bioavailability. However, increasing evidence suggests that diets providing adequate caloric intake may nevertheless remain biologically suboptimal if nutrient density and nutrient utilization are insufficient[22,23,58,86].

This distinction may be particularly important in the modern food environment, where ultra-processed foods (UPFs) often provide high caloric density with relatively low micronutrient density. Such dietary patterns may contribute to the paradoxical coexistence of caloric excess, obesity, and micronutrient insufficiency[87].

From a systems biology perspective, nutrient density should therefore be evaluated according to the capacity of foods to supply biologically usable nutrients relative to their caloric burden, metabolic effects, and overall physiological impact.

4.2. Protein Quality and Amino Acid Bioavailability

Protein quantity alone does not fully reflect nutritional quality. Proteins differ substantially in indispensable amino acid composition, digestibility, absorption efficiency, leucine content, nitrogen utilization, and capacity to stimulate muscle protein synthesis.

The Digestible Indispensable Amino Acid Score (DIAAS), increasingly recognized as a more accurate assessment of protein quality than the older Protein Digestibility Corrected Amino Acid Score (PDCAAS), incorporates digestibility of individual indispensable amino acids at the ileal level rather than relying solely on total fecal nitrogen absorption[36,88,89].

Many animal-source proteins generally demonstrate higher DIAAS values and greater bioavailability of indispensable amino acids compared with many plant proteins. Foods such as eggs, dairy, fish, and meat typically provide highly digestible proteins rich in leucine and other indispensable amino acids important for skeletal muscle maintenance, mitochondrial function, metabolic resilience, immune regulation, endocrine signaling, and tissue repair.

In contrast, many plant proteins may demonstrate lower digestibility and reduced concentrations of one or more indispensable amino acids, including lysine, methionine, or leucine, depending on the food source. In addition, naturally occurring antinutritional compounds such as phytates, tannins, lectins, and protease inhibitors may further reduce protein and mineral bioavailability in some plant foods.

This does not imply that plant-based diets are inherently inadequate. Rather, it suggests that nutritional adequacy in plant-exclusive dietary systems may require greater dietary diversity, complementary protein combinations, higher total protein intake, food preparation strategies that improve digestibility, and targeted supplementation in some individuals.

 doi:10.20944/preprints202605.0616.v1

These considerations may become increasingly important in aging populations, where anabolic resistance and sarcopenia increase protein and leucine requirements for preservation of skeletal muscle mass, mitochondrial function, and metabolic resilience.

Selected systems-level nutritional and toxicological characteristics of animal-derived and plant-derived foods are summarized in Table 1.

Table 1. ***Comparative Systems-Level Nutritional and Toxicological Characteristics of Animal-Derived and Plant-Derived Foods.***

Comparison of Key Characteristics of Animal-Derived vs. Plant-Derived Foods*

Dimension	Animal-Derived Foods (Overall Assessment)	Plant-Derived Foods (Overall Assessment)	Comparative Conclusion & Remarks
Nutrient Density (per 100 kcal)	↑ High — Rich in highly bioavailable nutrients	↓ Low–Moderate — Nutrient density lower in most plant foods	Animal foods provide more nutrients per unit energy.
Nutrient Completeness (Essential Nutrients)	↑ Complete — Contains all essential amino acids, B12, heme iron, DHA, etc.	↓ Incomplete — Often lack B12, DHA/EPA, heme iron, vitamin D, etc.	Animal foods are more nutritionally complete.
Vitamin A (Retinol Activity)	↑ Rich — Preformed retinol; highly bioavailable	↓ Limited — Provitamin A (carotenoids) requires conversion; lower efficiency	Vitamin A in animal foods is preformed and more bioavailable.
Vitamin K2 (MK-4 / MK-7)	↑ Present — MK-4 present in organ meats, egg yolks, full-fat dairy	↓ Very Low (mainly K1) — K2 (especially MK-4) largely absent	Animal sources are the most reliable K2 sources.
Vitamin B12	↑ Rich — Naturally present; high bioavailability	↓ Absent Naturally — Requires supplementation or fortified foods	B12 in animal foods; essential supplementation for plant-based diets.
Heme Iron (Bioavailability)	↑ Present (15–35% absorption) — Heme iron; higher absorption (15–35%)	↓ Non-Heme (2–10% absorption) — Lower absorption (2–10%) due to phytates, polyphenols	Heme iron in animal foods is absorbed more efficiently.
Omega-3 Fatty Acids (DHA/EPA)	↑ Rich — Preformed DHA and EPA; directly utilizable	↓ Minimal — ALA present; conversion to DHA/EPA is low (<1–5%)	Animal foods are the direct source of DHA/EPA.
Protein Quality (PDCAAS/DIAAS)	↑ High (0.90–1.00) — Complete amino acid profile; high digestibility	↓ Moderate (0.40–0.80) — Amino acid profile incomplete; lower digestibility	Animal proteins have superior overall quality and digestibility.
Dietary Fiber	↓ Low–Moderate — Generally low in total fiber	↑ High — Rich source of dietary fiber	Plant foods are the primary source of dietary fiber.
Natural Antinutrients & Plant Toxins	↓ Low–Moderate — Minimal antinutrients compared to plants	↑ Present — Contains phytates, lectins, oxalates, etc., that may reduce absorption	Plant antinutrients may impair mineral and protein absorption.
Caloric Density	↑ Higher — More energy dense	↓ Lower — Lower energy density	Animal foods are more calorie dense.
Satiety & Appetite Regulation	↑ Stronger — Protein and fat more effective for satiety	↓ Weaker — Requires larger volumes for satiety	Animal proteins and fats are more satiating.
Digestibility & Absorption	↑ High — High digestibility and bioavailability	↓ Moderate — Affected by fiber and antinutrients	Animal nutrients are more bioavailable.
Food Processing Burden	↑ Moderate — Risk from industrial processing in some products	↓ Lower (minimally processed) — Generally lower processing burden (whole foods)	Both food types can be affected by industrial processing.
Environmental Impact & Pollution Risk	↓ Higher — Higher resource use; greater pollution risk	↓ Lower — Lower resource use and environmental impact (in most cases)**	Plant-based diets generally have lower environmental impact.
Health Outcomes (Overall Evidence)	↑ Mixed–High — Supports muscle, bone, immune, and metabolic health	↑ Mixed–High — Benefits depend on diet quality and nutrient adequacy	Both food types can support health when appropriately designed.
Sustainability (Long-term Viability)	↓ Lower (in many cases)** — Higher land, water, and emissions footprint	↑ Higher (in most cases)** — More sustainable food system overall	Plant-based systems are generally more sustainable.
Toxicological Exposure Profile	↓ Greater concern for fat-soluble bioaccumulated toxicants, including POPs, dioxins, PCBs, and some marine-chain contaminants.	↓ Greater concern for water-soluble agricultural contaminants, pesticide/herbicide residues, nitrates, mycotoxins, and plant defense compounds.	Dietary systems may shift toxicological exposure profiles rather than eliminate toxic burden.

Integrated Conclusion: Animal-derived foods excel in nutrient density, bioavailability, and key micronutrients, whereas plant-derived foods excel in fiber, phytochemicals, excel in fiber, phytochemicality.

Optimal Health Strategy: Prioritize whole, minimally processed animal foods as the nutritional foundation, complemented by diverse plant-derived foods to achieve a comprehensive balance of nutrients, bioactive compounds, and long-term health outcomes.

* This table is based on current nutritional science, biochemistry, and clinical evidence.
** Environmental impact varies by production system, geography, and practices.
*** Vitamin A (Retinol): https://pubmed.ncbi.nlm.nih.gov/20200262/
**** ALA to DHA Conversion Efficiency: http://www.dhaomega3.org/Overview/Conversion-Efficiency-of-ALA-to-DHA-in-Humans

Abbreviations: ALA = α-Linolenic Acid; DHA = Docosahexaenoic Acid; EPA = Eicosapentaeenoic Acid; PDCAAS = Protein Digestibility–Corrected Amino Acid Score; DIAAS = Digestible Indispensable Amino Acid Score.

This table summarizes selected nutritional, metabolic, toxicological, and physiological characteristics commonly associated with animal-derived and plant-derived foods within the context of an IOM Systems Medicine framework. Comparisons are intended to illustrate general biological trends and systems-level considerations rather than absolute categorizations applicable to all foods or dietary patterns.

Nutritional quality may vary substantially according to food source, agricultural practices, environmental exposures, degree of processing, preparation methods, dietary composition, and individual physiological context.

Animal-derived foods generally provide highly bioavailable protein, vitamin B12, heme iron, DHA/EPA, vitamin K2, and other fat-soluble nutrients, whereas plant-derived foods may provide higher dietary fiber content, diverse phytochemicals, and lower environmental burden in some settings. Conversely, both food systems may also present distinct nutritional and toxicological limitations, including environmental contaminants, processing-related risks, nutrient insufficiencies, or naturally occurring bioactive defense compounds.

Importantly, the table further illustrates that plant-heavy and animal-heavy dietary systems may differ in dominant toxicological exposure profiles rather than being entirely "toxin-free." Plant-derived foods may involve relatively greater exposure to water-soluble agricultural contaminants, pesticide and herbicide residues, mycotoxins, nitrates, and plant defense compounds, whereas animal-derived foods may involve relatively greater exposure to fat-soluble bioaccumulated

 doi:10.20944/preprints202605.0616.v1

environmental pollutants including persistent organic pollutants (POPs), dioxins, PCBs, and certain marine-chain contaminants.

Accordingly, this comparison is intended as a systems-level framework for evaluating dietary compatibility, nutrient sufficiency, metabolic effects, mitochondrial support, toxicological burden, energetic resilience, and long-term physiological adaptability rather than support for any rigid dietary ideology.

4.3. Micronutrient Density and Biological Availability

Micronutrient density and nutrient bioavailability also differ considerably among foods. Certain animal-source foods provide highly bioavailable forms of nutrients including vitamin B12, heme iron, zinc, DHA/EPA, taurine, creatine, carnitine, retinol, and vitamin K2. These nutrients play important physiological roles in mitochondrial energy metabolism, oxygen transport, neurotransmitter synthesis, immune regulation, skeletal muscle maintenance, endocrine function, vascular biology, and cellular repair mechanisms.

Vitamin B12, for example, is naturally found almost exclusively in animal-source foods and is essential for neurological function, methylation pathways, erythropoiesis, and DNA synthesis. Similarly, heme iron from animal foods is generally absorbed more efficiently than non-heme iron from plant sources.

Long-chain omega-3 fatty acids such as DHA and EPA are also more directly available from fish and marine animal foods, whereas plant-derived alpha-linolenic acid (ALA) requires enzymatic conversion that may be relatively limited in humans.

Vitamin K2, particularly menaquinone forms such as MK-4 and MK-7, is found predominantly in animal foods and fermented products and may play important roles in vascular health, calcium regulation, and bone metabolism.

However, nutrient concentration alone does not guarantee physiological utilization. Mineral absorption may be strongly influenced by food matrix interactions and naturally occurring antinutritional compounds. For example, phytates may reduce absorption of zinc and iron, oxalates may reduce calcium bioavailability, and certain fiber interactions may alter mineral absorption in some dietary contexts [92–94].

Potential nutrients of concern in poorly designed plant-exclusive diets may include vitamin B12, DHA/EPA, zinc, iron, choline, vitamin K2, taurine, creatine, and carnitine. Deficiencies or insufficiencies in these nutrients may have implications for neurological function, mitochondrial metabolism, muscle maintenance, methylation pathways, endocrine signaling, immune regulation, and long-term metabolic resilience [95–97].

From an IOM Systems Medicine perspective, foods should therefore be evaluated not merely according to caloric content or isolated nutrient quantities, but according to their broader systems-level effects on nutrient sufficiency, metabolic efficiency, mitochondrial support, inflammatory regulation, biological resilience, toxicological burden, and long-term physiological adaptability.

Adequate nutrient density may also play an important role in supporting mitochondrial energetics, metabolic adaptability, recovery capacity, and long-term energetic resilience under conditions of physiological stress.

Within this framework, nutrient density and nutrient bioavailability become central determinants of dietary compatibility and long-term health.

5. Comparative Systems Analysis of Major Dietary Models

5.1. Standard American Diet (SAD)

The Standard American Diet (SAD) is characterized by ultra-processed foods (UPFs), refined carbohydrates, high glycemic load, industrially processed seed oils, excessive caloric density, low micronutrient density, reduced dietary fiber quality, frequent consumption of sugar-sweetened

 doi:10.20944/preprints202605.0616.v1

beverages, high sodium intake, disrupted omega-6 to omega-3 fatty acid ratios, and chronic hyperinsulinemic feeding patterns.

The SAD may represent one of the most profound dietary shifts in modern human history. Over the past century—and particularly since the mid-20th century—the human food environment has undergone substantial transformation through industrial food processing, large-scale carbohydrate refinement, widespread introduction of ultra-processed foods, and increasing replacement of traditional whole foods with highly engineered commercial products[22,23,90–92].

Modern ultra-processed foods are often specifically formulated for hyper-palatability, prolonged shelf stability, rapid consumption, stimulation of reward-related neurobehavioral pathways, and aggressive commercial scalability. These foods frequently combine refined starches, added sugars, industrial seed oils, emulsifiers, artificial flavor enhancers, and sodium in combinations that may dysregulate normal satiety signaling and promote excess caloric intake[90,91].

Increasing evidence suggests that ultra-processed food consumption is associated with obesity, insulin resistance, type 2 diabetes, cardiovascular disease, nonalcoholic fatty liver disease (NAFLD), hypertension, chronic inflammation, depression, and increased all-cause mortality[23,24,92–94]. Importantly, many of these associations persist even after adjustment for total caloric intake alone, suggesting that food quality and processing may independently influence metabolic physiology.

A landmark controlled feeding study by Hall et al. demonstrated that subjects consuming ultra-processed diets spontaneously consumed approximately 500 additional kcal/day compared with minimally processed diets despite matched macronutrient composition, resulting in significant weight gain over a short time period[23].

From a metabolic perspective, the SAD is typically characterized by repeated postprandial glucose and insulin excursions driven by frequent consumption of refined carbohydrates and sugar-containing foods. Chronic hyperinsulinemia may contribute to insulin resistance, adipocyte hypertrophy, hepatic de novo lipogenesis, visceral adiposity, endothelial dysfunction, mitochondrial stress, and chronic low-grade inflammation[4,68,95,96].

Continuous exposure to highly refined, rapidly absorbed carbohydrates may also impair the capacity for efficient fuel switching between glucose and fatty acid metabolism, thereby reducing energetic adaptability under conditions of metabolic stress.

Persistent hyperglycemia and hyperinsulinemia may also increase formation of advanced glycation end products (AGEs), oxidative stress, and inflammatory signaling pathways that contribute to vascular dysfunction and accelerated biological aging[4,96].

Industrial seed oils rich in omega-6 linoleic acid have also become increasingly dominant in the modern food supply. Although omega-6 fatty acids are physiologically essential, substantial increases in omega-6 consumption relative to omega-3 intake may influence inflammatory balance, lipid oxidation susceptibility, and membrane composition[69,97,98].

Simultaneously, reductions in consumption of whole foods, marine omega-3 sources, organ meats, fermented foods, and fiber-rich minimally processed foods may contribute to widespread micronutrient insufficiency despite caloric abundance. This phenomenon has contributed to the paradoxical coexistence of obesity, metabolic syndrome, and micronutrient deficiency within the same populations[99–103].

From an IOM Systems Medicine perspective, the SAD may be viewed as a systems-level dietary pattern that chronically promotes metabolic inflexibility, impaired energetic resilience, oxidative stress, mitochondrial dysfunction, endocrine dysregulation, inflammatory activation, impaired vascular integrity, altered gut microbiome ecology, and progressive loss of biological resilience.

Rather than representing merely an issue of excessive calories, the SAD may fundamentally represent a mismatch between modern industrialized food environments and human evolutionary metabolic physiology. Within this framework, chronic disease may emerge not from a single nutrient abnormality, but from cumulative systems-level disruption involving nutrient insufficiency, toxic burden, endocrine dysregulation, mitochondrial stress, impaired redox homeostasis, and chronic inflammatory signaling.

 doi:10.20944/preprints202605.0616.v1

5.2. Mediterranean Diet

The Mediterranean diet is among the most extensively studied dietary patterns in nutritional epidemiology and preventive medicine. Traditional Mediterranean dietary patterns, originally observed in regions bordering the Mediterranean Sea during the mid-20th century, have consistently been associated with lower cardiovascular risk, reduced inflammatory burden, improved metabolic health, lower incidence of type 2 diabetes, reduced all-cause mortality, and increased longevity[104–108].

Core characteristics of traditional Mediterranean dietary patterns generally include high intake of minimally processed vegetables, olive oil as the principal fat source, regular seafood consumption, legumes, nuts, herbs and spices, moderate fruit intake, moderate fermented dairy intake, relatively low intake of ultra-processed foods, and lower consumption of refined sugars and industrialized food products.

The Mediterranean diet is also characterized by greater phytonutrient diversity, higher polyphenol intake, increased monounsaturated fat consumption, higher omega-3 intake from marine foods, and increased dietary fiber from whole plant foods. Collectively, these dietary characteristics may contribute to improved endothelial function, reduced oxidative stress, enhanced insulin sensitivity, and lower chronic inflammatory signaling[106–110].

Olive oil, particularly extra virgin olive oil (EVOO), represents a central component of traditional Mediterranean dietary patterns. EVOO contains monounsaturated fatty acids, primarily oleic acid, along with polyphenols, tocopherols, and other bioactive compounds that may exert antioxidant, anti-inflammatory, and endothelial-supportive effects[110–112].

Marine foods commonly consumed in Mediterranean regions also provide DHA/EPA, selenium, taurine, iodine, and high-quality protein, which may further support cardiovascular, neurological, and metabolic health.

Substantial evidence suggests that Mediterranean dietary patterns may improve insulin sensitivity, lipid profiles, blood pressure, endothelial function, inflammatory biomarkers, and glycemic control in individuals with metabolic syndrome and type 2 diabetes[105,109,113]. In the PREDIMED trial, one of the largest randomized nutritional intervention studies ever conducted, Mediterranean dietary interventions supplemented with either extra virgin olive oil or nuts significantly reduced major cardiovascular events compared with low-fat dietary recommendations[105].

However, modern Mediterranean dietary implementations vary substantially across populations and commercial interpretations. Some contemporary Mediterranean-style diets may still contain relatively high carbohydrate loads, frequent grain consumption, breads, pasta, refined flour products, and significant total glycemic exposure.

For metabolically healthy and physically active individuals, such carbohydrate levels may be well tolerated. However, individuals with severe insulin resistance, obesity, metabolic syndrome, type 2 diabetes, NAFLD, or hyperinsulinemia may exhibit impaired carbohydrate tolerance and reduced metabolic flexibility[31,114–116].

In such individuals, even relatively “healthy” carbohydrate-rich Mediterranean dietary patterns may not adequately reduce insulin exposure, glycemic variability, hepatic fat accumulation, or chronic hyperinsulinemic signaling.

Emerging evidence suggests that lower-carbohydrate Mediterranean variants may produce greater improvements in glycemic control, triglycerides, HDL cholesterol, visceral adiposity, and metabolic syndrome parameters compared with higher-carbohydrate implementations[115–117].

Furthermore, many epidemiological studies evaluating Mediterranean dietary patterns were conducted in populations whose lifestyles differed substantially from modern sedentary industrial societies. Traditional Mediterranean populations often exhibited higher physical activity levels, lower ultra-processed food exposure, stronger social cohesion, greater sunlight exposure, lower

 doi:10.20944/preprints202605.0616.v1

chronic stress burden, and reduced environmental toxicant exposure. Therefore, beneficial outcomes associated with Mediterranean dietary patterns may partly reflect broader lifestyle and environmental factors beyond macronutrient composition alone.

From an IOM Systems Medicine perspective, the Mediterranean diet may be viewed as a relatively nutrient-dense and anti-inflammatory dietary framework that supports vascular integrity, mitochondrial function, metabolic and energetic resilience, microbiome diversity, and reduction of chronic inflammatory burden.

However, dietary suitability remains context-dependent. Optimal carbohydrate intake may vary considerably according to insulin sensitivity, metabolic status, mitochondrial function, physical activity, age, endocrine health, and individual genetic or epigenetic variability. Within this framework, the Mediterranean diet may serve as a beneficial foundational dietary model for many individuals, but may require modification—particularly carbohydrate reduction—in those with advanced metabolic dysfunction or severe insulin resistance.

5.3. Plant-Based and Vegan Diets

Plant-based and vegan dietary patterns have gained increasing popularity in recent decades due to ethical, environmental, religious, and perceived health considerations. These dietary models generally emphasize vegetables, fruits, legumes, whole grains, nuts, seeds, and plant-derived foods while minimizing or eliminating animal-source foods entirely.

Well-designed plant-based diets may offer several potential advantages, including higher phytonutrient intake, greater dietary fiber intake, lower intake of ultra-processed meats, lower caloric density, lower saturated fat intake in some implementations, improved insulin sensitivity, reduced LDL cholesterol, improved gut microbiome diversity, and favorable metabolic markers in certain populations[118–122].

Plant foods are major sources of polyphenols, flavonoids, carotenoids, vitamin C, folate, potassium, magnesium, and numerous phytochemicals with antioxidant and anti-inflammatory properties. Higher intake of minimally processed plant foods has been associated with reduced cardiovascular risk, lower blood pressure, and improved metabolic outcomes in epidemiological studies[119–123].

Importantly, however, the health effects of plant-based diets vary considerably according to food quality and degree of processing. Diets centered around refined grains, sugar-containing beverages, processed starches, industrial seed oils, vegan desserts, and ultra-processed meat substitutes may still promote hyperglycemia, chronic hyperinsulinemia, obesity, inflammation, and metabolic dysfunction[23,90,93].

Many modern vegan commercial products are highly processed and may contain refined starches, isolated seed oils, emulsifiers, flavor enhancers, additives, and synthetic ingredients while remaining relatively low in nutrient density and protein quality. Thus, a distinction should be made between whole-food plant-based diets and ultra-processed vegan dietary patterns.

One important nutritional consideration in plant-exclusive diets involves protein quality and amino acid bioavailability. Compared with many animal-source proteins, plant proteins often demonstrate lower DIAAS values, lower leucine content, reduced digestibility, and lower concentrations of one or more indispensable amino acids such as lysine or methionine[36,88,124,125].

These differences may become particularly important in aging populations, sarcopenia, chronic illness, athletic performance, recovery states, and metabolically stressed individuals. Reduced leucine availability may impair stimulation of muscle protein synthesis and anabolic signaling pathways important for maintenance of skeletal muscle mass, mitochondrial energetics, and metabolic resilience[36,124].

Micronutrient insufficiency may also occur in poorly planned vegan diets. Nutrients of particular concern may include vitamin B12, DHA/EPA, iron, zinc, choline, vitamin K2, iodine, selenium, taurine, creatine, and carnitine[126–131].

 doi:10.20944/preprints202605.0616.v1

Vitamin B12 deficiency is especially important because B12 is naturally found almost exclusively in animal-source foods. Inadequate B12 intake may contribute to anemia, neurological dysfunction, impaired methylation, elevated homocysteine, cognitive decline, and neuropathy[129]. Similarly, plant-derived non-heme iron is generally less bioavailable than heme iron from animal foods, while phytates may further impair zinc and iron absorption[126,128].

Long-chain omega-3 fatty acids DHA and EPA are largely absent from plant-exclusive diets unless algae-derived supplementation is used. Conversion of alpha-linolenic acid (ALA) to DHA in humans is relatively limited[130].

Another consideration involves naturally occurring plant defense compounds. Plants synthesize numerous chemical compounds for self-protection against insects, fungi, and predators, including lectins, oxalates, phytates, tannins, protease inhibitors, and certain alkaloids. Although many phytochemicals may confer health benefits in appropriate amounts, some antinutritional compounds may impair nutrient absorption or contribute to gastrointestinal irritation in susceptible individuals[132–134].

For example, phytates may reduce zinc and iron absorption, oxalates may reduce calcium bioavailability, and certain lectins may increase gastrointestinal irritation when inadequately prepared. Traditional food preparation methods such as soaking, fermentation, sprouting, pressure cooking, and thermal processing may reduce antinutrient burden and improve digestibility.

From an IOM Systems Medicine perspective, plant-based diets may provide important benefits when centered around minimally processed whole foods, metabolic flexibility, adequate protein intake, sufficient micronutrient support, and individualized nutritional planning. However, nutritional adequacy should not be assumed solely on the basis of plant exclusivity. Dietary quality, protein bioavailability, micronutrient sufficiency, metabolic tolerance, gastrointestinal resilience, and individual physiological demands remain central determinants of long-term health outcomes.

Within this framework, carefully designed plant-based diets may be effective for some individuals, but may require targeted supplementation, increased protein attention, metabolic personalization, and monitoring for nutritional insufficiencies, particularly in children, older adults, pregnant women, athletes, and individuals with chronic metabolic disease.

5.4. Low-Carbohydrate and Ketogenic Diets

Low-carbohydrate and ketogenic dietary patterns are characterized by reduction of dietary carbohydrate intake with relative increases in fat intake and, in some implementations, moderate protein intake. Although definitions vary, low-carbohydrate diets generally restrict carbohydrate intake sufficiently to reduce postprandial glucose and insulin excursions, while ketogenic diets further restrict carbohydrate intake to levels capable of inducing nutritional ketosis and increased hepatic ketone production[31,115,135,136].

Ketogenic diets promote production of ketone bodies including beta-hydroxybutyrate (BHB), acetoacetate, and acetone, which may serve as alternative metabolic fuels for the brain, skeletal muscle, myocardium, and other tissues during fasting or carbohydrate restriction.

From an evolutionary perspective, ketosis represents a normal physiological adaptation to reduced carbohydrate availability, fasting, food scarcity, or prolonged physical exertion rather than an inherently pathological state[115,135].

Low-carbohydrate and ketogenic diets may improve insulin sensitivity, glycemic control, metabolic flexibility, mitochondrial energetics, appetite regulation, triglyceride levels, HDL cholesterol, visceral adiposity, and inflammatory regulation in selected populations[33,114,117,136,137]. In individuals with insulin resistance and T2DM, carbohydrate restriction may substantially reduce the need for endogenous and exogenous insulin by lowering dietary glucose load and reducing chronic hyperinsulinemia [33,114,117,136–138].

Reduction in circulating insulin levels may have broad downstream physiological implications because insulin functions not only as a glucose-regulating hormone, but also as a major anabolic and signaling molecule influencing adipocyte metabolism, hepatic lipogenesis, inflammation, endothelial

 doi:10.20944/preprints202605.0616.v1

biology, mitochondrial signaling, and nutrient partitioning. Improved metabolic flexibility—the ability to efficiently transition between glucose and fat oxidation—may therefore represent one of the key physiological benefits of carbohydrate restriction[137,138].

From a systems physiology perspective, ketogenic metabolism may also enhance aspects of energetic resilience by improving the capacity to utilize fatty acids and ketone bodies during fasting, prolonged exertion, fluctuating nutrient availability, and metabolic stress. This adaptive fuel-switching capacity may have represented an important evolutionary survival mechanism during periods of intermittent food scarcity and high physical demand.

Ketone bodies themselves may also function as signaling molecules. Beta-hydroxybutyrate has been shown to influence oxidative stress regulation, inflammatory pathways, mitochondrial biogenesis, histone deacetylase inhibition, and cellular stress resistance mechanisms[13,47,139]. Emerging evidence suggests that nutritional ketosis may reduce reactive oxygen species production per unit ATP generated under certain conditions, potentially improving aspects of mitochondrial energetic efficiency[13].

Therapeutic ketosis has demonstrated clinical utility in several neurological and metabolic disorders. Ketogenic diets have long been used in refractory epilepsy and may reduce seizure frequency through mechanisms involving altered neurotransmitter balance, mitochondrial stabilization, reduced neuronal excitability, and enhanced bioenergetic resilience[140,141].

More recently, ketogenic interventions have been investigated in obesity, metabolic syndrome, neurodegenerative disease, polycystic ovary syndrome (PCOS), migraine disorders, traumatic brain injury, and potentially cancer metabolism[62,142–146]. Interest in ketogenic therapy for neurodegenerative disorders such as Alzheimer's disease partly derives from evidence suggesting impaired cerebral glucose metabolism in affected individuals. Ketones may provide an alternative fuel source for neurons under conditions of glucose hypometabolism[144].

In oncology research, ketogenic diets have attracted attention because many tumors exhibit increased glucose dependence and altered mitochondrial metabolism, often described as part of the Warburg phenotype. Nutritional ketosis may theoretically influence glucose availability, insulin signaling, IGF-1 signaling, oxidative stress balance, and tumor metabolic flexibility[34,146,147].

However, evidence remains heterogeneous and cancer responses likely vary substantially according to tumor type, metabolic phenotype, mitochondrial function, genomic characteristics, host nutritional status, and treatment context.

Within IOM Systems Medicine, ketogenic therapy is viewed not merely as carbohydrate restriction, but as part of a broader systems-level metabolic intervention aimed at restoring metabolic flexibility, insulin regulation, mitochondrial function, oxidative balance, inflammatory control, and vascular integrity.

However, poorly designed ketogenic diets may also involve important risks and limitations. Some commercial ketogenic implementations rely heavily on processed meats, refined oils, artificial sweeteners, ultra-processed "keto" products, nutrient-poor fats, and low-quality animal products. Such approaches may lead to micronutrient imbalance, inadequate fiber intake, gastrointestinal dysfunction, excessive saturated fat intake in susceptible individuals, reduced phytonutrient diversity, and poor long-term dietary sustainability[33,148,149].

In addition, because many environmental toxicants are lipophilic, high intake of contaminated animal fats may increase exposure to persistent organic pollutants (POPs), heavy metals, dioxins, PCBs, and fat-soluble environmental toxins, particularly when food quality is poor[150,151].

From an IOM Systems Medicine perspective, ketogenic diets may offer powerful therapeutic potential when implemented using nutrient-dense whole foods, adequate micronutrient support, sufficient mineral intake, high-quality protein, anti-inflammatory fats, seafood-derived omega-3 sources, and careful metabolic monitoring.

Within this framework, ketosis represents not simply a dietary trend, but a physiological metabolic state that may restore aspects of mitochondrial energetics, metabolic adaptability, energetic resilience, and systemic metabolic regulation in appropriately selected individuals.

 doi:10.20944/preprints202605.0616.v1

5.5. Carnivore and Elimination-Based Dietary Approaches

Carnivore-based and elimination-style dietary approaches have emerged in recent years as potential therapeutic interventions in selected individuals with autoimmune disorders, chronic inflammatory conditions, gastrointestinal syndromes, severe food sensitivities, metabolic dysfunction, and refractory immune-mediated symptoms.

These dietary models generally involve substantial reduction or complete elimination of grains, legumes, seed oils, processed foods, refined sugars, and, in stricter carnivore implementations, nearly all plant foods. Carnivore diets typically emphasize ruminant meats, seafood, eggs, animal fats, and, in some implementations, dairy products.

Although formal clinical evidence remains limited, anecdotal reports, observational surveys, and emerging mechanistic hypotheses suggest potential symptomatic improvement in selected individuals with chronic inflammatory or immune-mediated disorders[152–155].

Proposed mechanisms may include removal of plant defense compounds, reduction of glycemic burden, elimination of food allergens, reduced dietary antigen exposure, decreased intake of ultra-processed foods, simplified dietary exposures, improved satiety signaling, stabilization of blood glucose, and reduction of gastrointestinal irritants.

From a systems biology perspective, elimination diets may reduce cumulative exposure to dietary variables capable of provoking immune activation, gastrointestinal permeability, dysbiosis, mast cell activation, or chronic inflammatory signaling in susceptible individuals.

One proposed mechanism involves removal of certain naturally occurring plant defense compounds. Plants synthesize numerous bioactive chemicals for protection against insects, fungi, and predators, including lectins, oxalates, phytates, tannins, salicylates, alkaloids, and protease inhibitors. Although many phytochemicals may exert beneficial effects in appropriate physiological contexts, some individuals may demonstrate heightened sensitivity to particular compounds, potentially contributing to gastrointestinal irritation, altered intestinal permeability, immune activation, or inflammatory symptoms[132,133,154,155].

For example, lectins may interact with intestinal epithelial surfaces, oxalates may contribute to kidney stone formation or tissue deposition in susceptible individuals, and certain fermentable carbohydrates may exacerbate gastrointestinal symptoms in patients with irritable bowel syndrome (IBS) or small intestinal bacterial overgrowth (SIBO). Elimination-based approaches may therefore function, in part, as diagnostic tools to identify food intolerances or immune-triggering dietary components.

Reduction of glycemic burden may represent another important mechanism. Many carnivore and animal-based diets are inherently low in carbohydrates and may therefore reduce postprandial glucose excursions, lower insulin secretion, improve metabolic flexibility, reduce hyperinsulinemia, and improve metabolic fuel stability in selected individuals. These metabolic effects overlap substantially with those observed in ketogenic and low-carbohydrate dietary interventions[31,136,137].

Some individuals with obesity, metabolic syndrome, T2DM, autoimmune disease, or chronic inflammatory disorders may experience symptomatic improvements associated with stabilization of glucose and insulin dynamics.

Carnivore-style elimination diets may also reduce overall dietary complexity and exposure to food additives, emulsifiers, artificial sweeteners, preservatives, industrial seed oils, and ultra-processed food ingredients. Emerging evidence suggests that some food additives and emulsifiers may influence gut microbiome composition, intestinal barrier integrity, mucosal immunity, and inflammatory signaling pathways[156,157].

Thus, symptomatic improvements observed in some individuals may not necessarily derive solely from elimination of plant foods, but also from simultaneous removal of ultra-processed foods and industrialized dietary exposures.

However, important concerns and uncertainties remain regarding long-term carnivore dietary patterns. Long-term clinical outcome data are currently sparse, and most available evidence consists

 doi:10.20944/preprints202605.0616.v1

primarily of case reports, observational surveys, mechanistic hypotheses, and anecdotal experiences rather than randomized long-term controlled trials.

Potential concerns may include reduced phytonutrient diversity, inadequate fiber intake, altered microbiome ecology, micronutrient imbalance in poorly designed implementations, excessive processed meat intake, excessive saturated fat intake in susceptible individuals, and increased exposure to environmental toxicants concentrated in animal fats[150,158–160].

Additionally, dietary tolerance likely varies substantially according to genetics, microbiome composition, immune status, metabolic health, toxin burden, gastrointestinal integrity, and individual nutrient requirements.

From an IOM Systems Medicine perspective, carnivore and elimination-based diets may be best understood not as universal dietary prescriptions, but as targeted therapeutic tools that may reduce immunological, gastrointestinal, and metabolic burden in selected individuals.

Within this framework, dietary responses should be evaluated according to symptom resolution, metabolic outcomes, inflammatory markers, nutrient sufficiency, mitochondrial function, gastrointestinal resilience, and long-term physiological adaptability rather than ideological assumptions alone.

At present, long-term evidence remains limited, and additional mechanistic studies, controlled clinical trials, and long-term outcome research are required to better define efficacy, safety, optimal implementation strategies, patient selection, and long-term physiological consequences of carnivore-based dietary interventions.

Comparative systems-level characteristics of major dietary patterns discussed in this review are summarized in Table 2. The proposed transition from ancestral metabolic flexibility toward chronic glucose dependency and reduced energetic resilience in the modern environment is illustrated in Figure 2.

Table 2. ***Systems-Level Comparison of Common Dietary Patterns.*** *This* table summarizes selected systems-level characteristics commonly associated with major dietary patterns discussed within the IOM Systems Nutrition Framework, including the Standard American Diet (SAD), Mediterranean, whole-food plant-based/vegan, low-carbohydrate, ketogenic, and carnivore/elimination-based dietary approaches. Comparisons are intended to illustrate general metabolic, nutritional, physiological, and toxicological trends rather than absolute conclusions applicable to all individuals or dietary implementations. Dietary quality may vary substantially according to food sourcing, degree of processing, nutrient composition, environmental exposures, lifestyle factors, and individual metabolic or physiological context. The framework emphasizes that no single dietary model is universally optimal under all conditions. Rather, dietary systems may differ in their effects on glycemic burden, nutrient sufficiency, mitochondrial energetics, metabolic flexibility, energetic resilience, inflammatory regulation, toxicological burden, and long-term physiological adaptability. Accordingly, this comparison is intended as a systems-level analytical framework for evaluating dietary compatibility with human physiology rather than support for rigid dietary ideology or universal dietary prescriptions.

 doi:10.20944/preprints202605.0616.v1

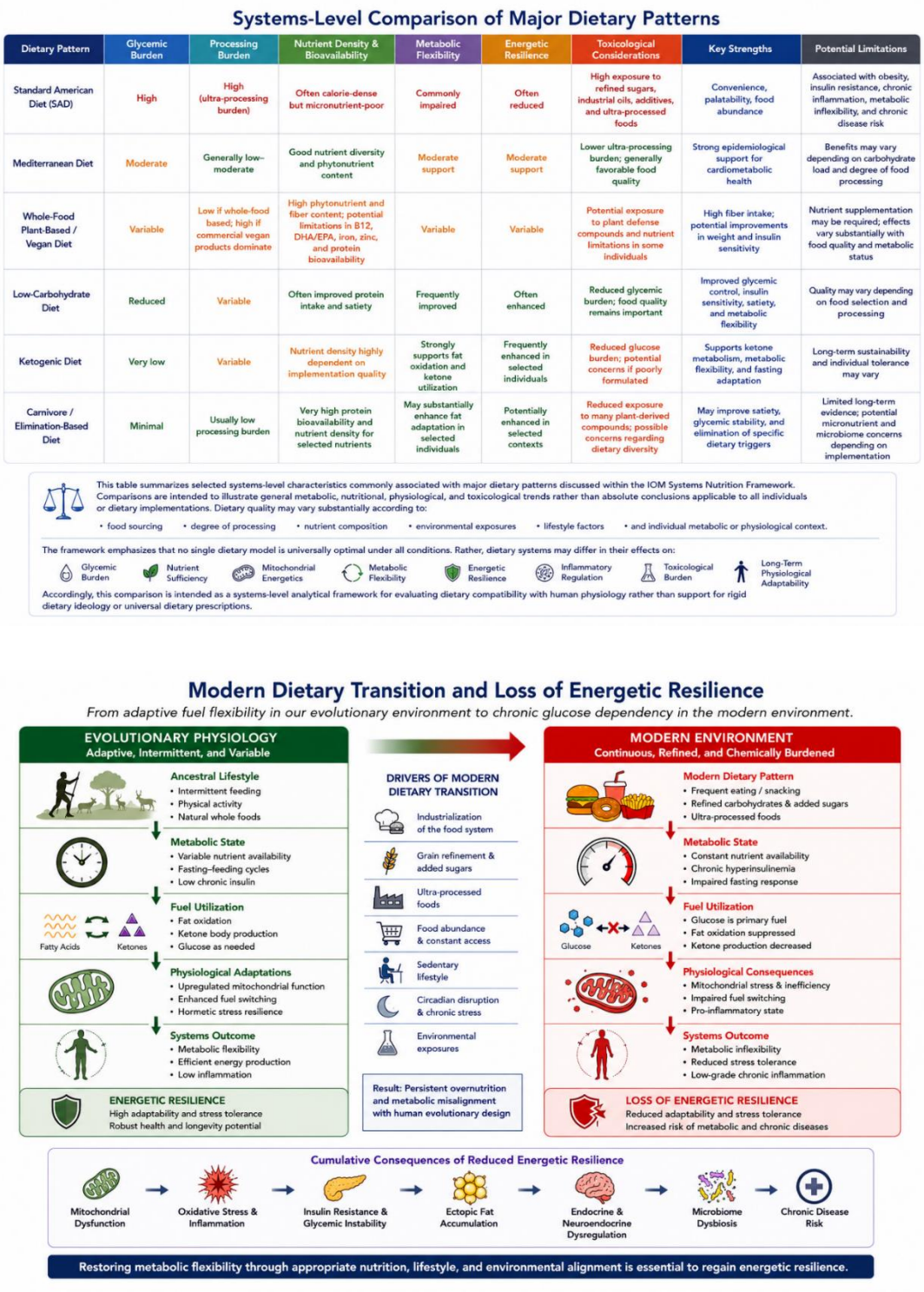

Figure 2. ***Modern Dietary Transition and Loss of Energetic Resilience.*** This figure illustrates a proposed systems-level model describing the transition from ancestral patterns of intermittent feeding and adaptive fuel utilization toward modern dietary environments characterized by continuous food availability, refined carbohydrates, ultra-processed foods, reduced physical activity, circadian disruption, and increased environmental toxicological burden. Under ancestral physiological conditions, fluctuating nutrient availability and intermittent fasting promoted metabolic flexibility, fatty acid oxidation, ketone utilization, mitochondrial adaptability, and energetic resilience. In contrast, modern dietary patterns characterized by chronic hyperinsulinemia, persistent glucose exposure, reduced fasting periods, and highly processed food intake may contribute to impaired fuel switching, mitochondrial stress, reduced metabolic flexibility, and diminished physiological adaptability. The model further proposes that chronic loss of energetic resilience may contribute to interconnected downstream

 doi:10.20944/preprints202605.0616.v1

disturbances including oxidative stress, inflammation, insulin resistance, ectopic fat accumulation, neuroendocrine dysregulation, microbiome disruption, and increased chronic disease susceptibility. From an IOM Systems Medicine perspective, restoration of metabolic flexibility and energetic resilience through appropriate nutrition, physical activity, circadian regulation, and reduction of cumulative toxicological burden may represent important strategies for long-term systems-level health maintenance.

6. Plant Defense Compounds and Nutritional Toxicology

6.1. Plants as Biological Defense Systems

Plants are sessile organisms that cannot escape environmental threats through movement. As a result, they have evolved highly sophisticated biological defense systems to protect themselves against insects, fungi, bacteria, herbivores, ultraviolet radiation, oxidative stress, and environmental injury.

These defense mechanisms include production of a broad range of bioactive chemical compounds commonly referred to as antinutrients, phytochemicals, secondary metabolites, or plant defense compounds. Such compounds may exert beneficial, neutral, or harmful physiological effects depending on biological context and exposure conditions[134,154,155,157,161].

Major classes of plant defense compounds include lectins, oxalates, phytates, alkaloids, phytoestrogens, salicylates, tannins, cyanogenic glycosides, glucosinolates, protease inhibitors, saponins, and gluten-related proteins. These compounds often function in plants as insect deterrents, antifungal agents, signaling molecules, oxidative stress protectants, bitter-taste deterrents, or anti-predation chemicals[134,154,157,161].

Importantly, plant defense compounds should not automatically be categorized as universally harmful. Many phytochemicals may exert antioxidant, anti-inflammatory, antimicrobial, hormetic, and signaling effects that provide physiological benefits under appropriate conditions and doses. For example, polyphenols may activate cellular stress-response pathways, sulforaphane from cruciferous vegetables may stimulate detoxification enzymes, and certain flavonoids may modulate inflammatory signaling pathways[162–165].

This concept is sometimes described within the framework of hormesis, in which mild biological stressors may stimulate adaptive cellular resilience pathways under appropriate physiological conditions.

However, biological effects are highly context-dependent and may vary substantially according to dose, preparation methods, gut integrity, microbiome composition, immune status, metabolic health, genetic polymorphisms, developmental stage, and individual susceptibility. Thus, compounds that may be tolerated or beneficial in one individual may provoke adverse reactions in another.

Lectins are carbohydrate-binding proteins present in many plants including legumes, grains, nightshades, and seeds. Certain lectins may resist digestion and interact with intestinal epithelial surfaces. Experimental studies suggest that some lectins may influence intestinal permeability, immune activation, inflammatory signaling, and epithelial barrier function under specific conditions[155]. However, cooking, soaking, fermentation, sprouting, and pressure cooking may substantially reduce lectin activity in many foods.

Oxalates are organic acids found in foods such as spinach, almonds, beet greens, rhubarb, chocolate, and sweet potatoes. In susceptible individuals, excessive oxalate intake may contribute to kidney stone formation, calcium binding, reduced mineral absorption, or tissue oxalate accumulation. Calcium intake, gut microbiome composition, intestinal absorption, hydration status, and renal function may substantially influence oxalate metabolism and risk[133,166].

Phytates (phytic acid), commonly found in grains, legumes, nuts, and seeds, function as phosphorus storage molecules in plants. Phytates may bind minerals including zinc, iron, calcium, and magnesium, thereby reducing mineral bioavailability under some conditions[128,132].

 doi:10.20944/preprints202605.0616.v1

However, phytates may also exhibit antioxidant and potential anticancer properties, again illustrating the context-dependent nature of plant defense compounds.

Traditional food preparation methods such as fermentation, soaking, sprouting, and sourdough processing may significantly reduce phytate concentrations and improve mineral absorption.

Phytoestrogens, particularly isoflavones found in soy products, may interact with estrogen receptors and influence endocrine signaling. Their physiological effects remain complex and may vary according to hormonal status, age, gut microbiome composition, sex, dosage, and metabolic context[167,168].

Similarly, salicylates naturally present in many fruits, herbs, and vegetables may provoke symptoms in susceptible individuals with salicylate sensitivity or mast cell activation disorders.

Gluten-related proteins found in wheat, barley, and rye may trigger autoimmune responses in genetically susceptible individuals with celiac disease. Emerging evidence also suggests that a subset of individuals may experience non-celiac gluten sensitivity involving gastrointestinal symptoms, neurological symptoms, immune activation, or inflammatory responses[169–171].

From an IOM Systems Medicine perspective, plant defense compounds should neither be simplistically demonized nor universally idealized. Their physiological effects are best understood within a systems-based framework integrating exposure dose, food preparation, gastrointestinal integrity, microbiome ecology, immune tolerance, mitochondrial and energetic resilience, detoxification capacity, metabolic flexibility, and individual biological variability.

Within this framework, nutritional toxicology becomes highly individualized. Foods that support health in one physiological context may contribute to inflammatory burden or intolerance in another. Consequently, dietary evaluation should move beyond rigid ideological classifications toward personalized assessment of tolerance, nutrient sufficiency, inflammatory response, metabolic effects, and long-term physiological adaptability.

6.2. Oxalates and Metabolic Burden

Oxalates (oxalic acid and oxalate salts) are naturally occurring organic compounds synthesized by many plants as part of their defense and metabolic regulatory systems. In plants, oxalates may function in mineral regulation, calcium storage, defense against herbivores, heavy metal detoxification, and oxidative stress responses[172,173].

In human nutrition, oxalates are widely distributed throughout the food supply, but concentrations vary substantially among foods. Certain plant foods contain particularly high levels of oxalates, including spinach, almonds, rhubarb, beet greens, Swiss chard, sweet potatoes, dark chocolate, turmeric, peanuts, and soy products.

Oxalate content may also vary according to plant species, growing conditions, soil composition, food processing, cooking methods, and preparation techniques.

Under normal physiological conditions, oxalates may be partially degraded by intestinal microbiota, excreted through the kidneys, or bound to calcium within the gastrointestinal tract and eliminated in stool. However, excessive oxalate exposure, increased intestinal absorption, impaired microbial degradation, or altered renal handling may contribute to pathological oxalate accumulation in susceptible individuals[133,173–175].

In susceptible individuals, excessive oxalate exposure may contribute to kidney stone formation, tissue crystal deposition, inflammatory responses, oxidative stress, epithelial injury, mineral binding, gastrointestinal irritation, and mitochondrial stress.

Calcium oxalate represents the most common constituent of kidney stones worldwide. Oxalate may bind calcium in urine and form insoluble calcium oxalate crystals capable of inducing renal tubular injury, inflammatory activation, oxidative stress generation, and urinary obstruction[174–178].

Emerging evidence suggests that oxalates may exert biological effects beyond nephrolithiasis alone. Experimental studies indicate that calcium oxalate crystals may activate inflammatory

 doi:10.20944/preprints202605.0616.v1

cytokine pathways, NLRP3 inflammasome signaling, macrophage activation, reactive oxygen species production, and mitochondrial dysfunction[174,179,180].

Oxalate-induced oxidative stress may impair mitochondrial membrane function, ATP production, calcium homeostasis, and cellular redox balance under certain conditions. These mechanisms have led some investigators to hypothesize that chronic oxalate burden may potentially contribute to broader systemic inflammatory or metabolic effects in susceptible individuals, although large-scale clinical evidence remains limited.

Oxalate metabolism is strongly influenced by intestinal physiology and microbiome composition. Certain gut bacteria, particularly *Oxalobacter formigenes*, are capable of degrading oxalates within the gastrointestinal tract and reducing oxalate absorption[181].

Disruption of gut microbiome ecology through antibiotics, gastrointestinal disease, inflammatory bowel disorders, bariatric surgery, chronic dysbiosis, or intestinal permeability disorders may increase oxalate absorption and systemic oxalate burden. Increased intestinal permeability ("leaky gut") may further enhance oxalate uptake in susceptible individuals[154,182,183].

Importantly, susceptibility to oxalate-related pathology varies considerably among individuals. Factors influencing oxalate tolerance may include gut microbiome composition, calcium intake, hydration status, renal function, vitamin B6 status, magnesium status, mitochondrial resilience, gastrointestinal integrity, genetic polymorphisms, and total dietary oxalate load.

Food preparation methods may also significantly influence oxalate exposure. Boiling certain vegetables, for example, may substantially reduce soluble oxalate content through leaching into cooking water[184]. Additionally, simultaneous calcium intake during meals may reduce intestinal oxalate absorption by promoting formation of insoluble calcium oxalate complexes within the gut lumen[133].

From an IOM Systems Medicine perspective, oxalates may represent an example of how naturally occurring plant defense compounds can exert highly individualized biological effects depending on exposure burden, detoxification capacity, microbiome ecology, mineral balance, gastrointestinal integrity, and mitochondrial function.

Within this framework, oxalate-related pathology should not be viewed as universally applicable to all individuals consuming plant foods. Rather, oxalate tolerance likely exists along a spectrum influenced by systems-level physiological resilience and cumulative metabolic burden.

Accordingly, personalized nutritional assessment may become particularly important in individuals with recurrent kidney stones, chronic inflammatory syndromes, gastrointestinal disorders, mitochondrial dysfunction, autoimmune disease, vulvodynia, fibromyalgia, or unexplained multisystem inflammatory symptoms potentially associated with altered oxalate handling.

These observations further illustrate that nutritional tolerance and toxicological burden are highly individualized and may depend on systems-level interactions among diet, metabolism, microbiome ecology, mitochondrial function, and host adaptive capacity.

Although mechanistic and observational evidence exists, large-scale controlled clinical evidence remains limited for many proposed systemic oxalate-related syndromes.

7. Reframing Dietary Toxicology

7.1. No Modern Food System Is Toxin-Free

Modern dietary discourse often selectively emphasizes toxicological risks associated with particular food categories while minimizing others. Public debate frequently polarizes around simplified narratives such as "animal foods are toxic," "plant foods are toxic," "fat is harmful," or "carbohydrates are harmful," while underappreciating the broader complexity of modern environmental and nutritional toxicology.

 doi:10.20944/preprints202605.0616.v1

In reality, no modern dietary system is entirely free of toxicological burden. Human beings now exist within an industrialized ecological environment characterized by widespread exposure to environmental pollutants, agricultural chemicals, industrial food processing compounds, microplastics, heavy metals, endocrine-disrupting chemicals, persistent organic pollutants (POPs), air pollution, and cumulative metabolic stressors[26,28,29,150,185].

Consequently, toxicological exposure should not be conceptualized as a binary phenomenon ("toxic" versus "non-toxic"), but rather as a systems-level continuum influenced by cumulative physiological burden and adaptive capacity, including exposure duration, dose, nutrient status, mitochondrial resilience, detoxification capacity, microbiome integrity, inflammatory status, and genetic susceptibility.

Modern food systems may expose individuals to toxicological burdens through multiple pathways, including pesticide residues, herbicides, fungicides, industrial seed oil oxidation products, advanced glycation end products (AGEs), heavy metals, food additives, plastic-associated chemicals, ultra-processed food compounds, microbial contaminants, and environmental pollutants bioaccumulated through the food chain.

Both plant and animal foods may accumulate toxicants depending on soil quality, water contamination, agricultural practices, industrial pollution, food processing methods, packaging materials, and environmental bioaccumulation patterns[156,186–188].

For example, large predatory fish may accumulate mercury, animal fats may concentrate lipophilic persistent organic pollutants, rice may accumulate arsenic, leafy vegetables may contain pesticide residues, and ultra-processed foods may contain emulsifiers, preservatives, and packaging-derived contaminants.

Importantly, toxicological burden may arise not only from exogenous toxins, but also from endogenous metabolic dysfunction. Chronic hyperglycemia, insulin resistance, mitochondrial dysfunction, and oxidative stress may generate reactive oxygen species (ROS), lipid peroxidation products, inflammatory cytokines, advanced glycation end products, and metabolic byproducts capable of contributing to tissue injury and accelerated aging[4,96,189,190]. Thus, metabolic dysregulation itself may function as an internal toxicological environment.

Mitochondrial function may play a central role in determining cellular resilience to cumulative toxicological exposure through regulation of oxidative balance, energy production, and adaptive stress responses. Within this framework, the distinction between external toxic burden and internally generated metabolically derived toxicological stress becomes increasingly interconnected.

Modern ultra-processed food systems may further amplify toxicological burden through excessive caloric density, nutrient dilution, altered satiety signaling, oxidized industrial oils, food additives, artificial flavoring systems, and chronic overactivation of reward pathways. Such dietary patterns may simultaneously increase toxic exposure, reduce micronutrient sufficiency, impair mitochondrial function, alter microbiome ecology, and weaken endogenous detoxification systems[23,90,92,93].

Importantly, toxicological susceptibility likely varies substantially among individuals according to genetics, age, developmental exposure, nutrient status, detoxification capacity, mitochondrial function, microbiome diversity, endocrine health, and cumulative lifetime exposure burden.

From an IOM Systems Medicine perspective, dietary toxicology should therefore be reframed away from simplistic ideological categorizations toward a broader systems-level assessment integrating toxic burden, nutrient density, mitochondrial resilience, metabolic flexibility, inflammatory regulation, endocrine stability, detoxification capacity, microbiome integrity, and biological adaptability.

Within this framework, the central question may not be whether a particular dietary pattern is completely toxin-free—because no modern dietary system is entirely devoid of toxicological burden—but rather whether the overall dietary pattern reduces cumulative physiological stress, supports detoxification systems, maintains nutrient sufficiency, preserves mitochondrial function, and enhances long-term biological resilience.

 doi:10.20944/preprints202605.0616.v1

7.2. Water-Soluble Versus Fat-Soluble Toxins

Different dietary systems may shift toxicological exposure profiles rather than eliminate toxicity altogether. Modern debates surrounding nutrition frequently frame specific dietary models as either "clean" or "toxic," yet from a systems biology perspective, virtually all contemporary food systems exist within an increasingly industrialized and chemically exposed ecological environment.

Accordingly, different dietary patterns may preferentially alter the type of toxicological exposure, tissue distribution, storage characteristics, metabolic processing, and detoxification demands rather than completely eliminating toxic burden itself.

One useful conceptual framework involves distinguishing between predominantly water-soluble toxicants and predominantly fat-soluble toxicants. These categories differ substantially in absorption, tissue distribution, bioaccumulation, elimination pathways, and long-term biological persistence.

Plant-heavy dietary systems may involve greater exposure to pesticide residues, herbicides, glyphosate, nitrates, heavy metals from soil, water-soluble agricultural contaminants, mycotoxins, and naturally occurring plant defense compounds. Such compounds are often introduced through industrial agriculture, fertilizer use, herbicide application, contaminated irrigation systems, food storage conditions, and environmental pollution.

Many of these compounds are relatively water-soluble and may exert toxicological effects through oxidative stress, endocrine disruption, mitochondrial dysfunction, microbiome disruption, epithelial barrier injury, and chronic inflammatory signaling[191–196].

For example, glyphosate exposure has been investigated for potential effects on microbiome ecology and mineral chelation, nitrates may contribute to nitrosamine formation under some conditions, and pesticide residues may exert endocrine-disrupting or mitochondrial effects depending on dose and cumulative exposure burden.

Additionally, many plant foods contain naturally occurring defense compounds—including lectins, oxalates, phytates, alkaloids, and salicylates—which may further contribute to toxicological or immunological burden in susceptible individuals.

Conversely, animal-heavy dietary systems may involve greater exposure to persistent organic pollutants (POPs), dioxins, polychlorinated biphenyls (PCBs), organochlorine compounds, heavy metals, and fat-soluble bioaccumulated toxins.

Because many environmental pollutants are lipophilic, they may accumulate progressively within adipose tissue, animal fats, marine food chains, dairy products, and organs of long-lived animals. Large predatory fish, for example, may accumulate mercury, PCBs, and industrial pollutants through biomagnification across trophic levels[26,150,185,186,197].

Unlike many water-soluble compounds that may be more readily excreted, fat-soluble toxicants may persist in human tissues for years or decades due to storage within adipose tissue, enterohepatic recirculation, slow metabolic clearance, and cumulative environmental exposure.

These compounds have been associated with endocrine disruption, insulin resistance, mitochondrial dysfunction, carcinogenesis, neurotoxicity, reproductive dysfunction, and chronic inflammatory activation[26,185,197,198].

Importantly, toxicological risk is not determined solely by dietary category, but also by food sourcing, agricultural practices, environmental contamination, food processing, cooking methods, nutrient sufficiency, detoxification capacity, microbiome integrity, mitochondrial resilience, and cumulative lifetime exposure burden.

For example, regenerative agricultural practices may reduce certain toxic exposures, grass-fed animal systems may differ from industrial feedlot systems, organic cultivation may reduce some pesticide exposures, and food preparation techniques may alter toxicological burden.

At the same time, nutrient status itself strongly influences toxicological resilience. Adequate intake of glutathione-supportive nutrients, selenium, zinc, magnesium, vitamin C, sulfur-containing amino acids, and phytonutrients may substantially influence detoxification capacity and oxidative stress resilience[199–201]. From an IOM Systems Medicine perspective, the central question therefore

 doi:10.20944/preprints202605.0616.v1

becomes not whether a food system is toxin-free, but whether total toxicological burden exceeds biological resilience, energetic adaptability, and detoxification capacity.

Within this framework, chronic disease risk may emerge not from a single "toxic food," but from cumulative systems-level imbalance involving toxic exposure burden, nutrient insufficiency, mitochondrial dysfunction, impaired detoxification, chronic inflammatory activation, endocrine disruption, microbiome dysregulation, and loss of metabolic flexibility.

Accordingly, nutritional toxicology should move beyond simplistic ideological food categorizations toward individualized systems-level assessment of exposure load, detoxification capacity, inflammatory resilience, metabolic adaptability, and long-term physiological reserve.

8. Toward an IOM Systems Nutrition Framework

This paper proposes that optimal human nutrition should be evaluated not according to rigid dietary ideology, but according to integrated systems-level effects on metabolic regulation, mitochondrial energetics, inflammatory burden, endocrine signaling, detoxification capacity, vascular integrity, immune balance, and long-term biological resilience.

From an IOM Systems Medicine perspective, the central nutritional question is not whether a diet is "plant-based," "animal-based," "low-fat," or "low-carbohydrate," but whether the overall dietary system supports restoration and maintenance of physiological homeostasis under modern environmental conditions.

Within this framework, healthy dietary systems should ideally emphasize the following interconnected principles.

8.1. Low Glycemic Burden

Chronic hyperglycemia and hyperinsulinemia may represent central drivers of modern metabolic disease. Excessive glycemic load may contribute to insulin resistance, endothelial dysfunction, oxidative stress, advanced glycation end product (AGE) formation, mitochondrial overload, chronic inflammation, and accelerated biological aging[4,31,95,96,136].

Repeated postprandial glucose and insulin excursions may progressively impair metabolic flexibility, adipocyte regulation, hepatic metabolism, vascular integrity, and pancreatic beta-cell function. Accordingly, reducing chronic glycemic burden may improve insulin sensitivity, glycemic stability, mitochondrial function, inflammatory regulation, and long-term cardiometabolic outcomes.

Importantly, optimal carbohydrate tolerance likely varies substantially according to insulin sensitivity, physical activity, mitochondrial function, age, metabolic health, and genetic or epigenetic variability.

8.2. Low Processing Burden

Ultra-processed industrial foods may contribute substantially to modern chronic disease burden through excessive caloric density, nutrient dilution, altered satiety signaling, hyperpalatability, industrial additives, oxidized oils, emulsifiers, and microbiome disruption[23,156,157,202].

Modern ultra-processed foods often combine refined starches, sugars, industrial seed oils, flavor enhancers, and artificial additives in ways that may dysregulate appetite regulation and metabolic signaling.

Emerging evidence suggests that food processing itself—not merely macronutrient composition—may independently influence obesity risk, inflammatory burden, insulin resistance, gut barrier integrity, mitochondrial stress, and cardiometabolic health.

Accordingly, minimizing ultra-processed foods and emphasizing minimally processed nutrient-dense foods may represent a foundational principle of systems nutrition.

 doi:10.20944/preprints202605.0616.v1

8.3. Low Pollution Burden

Modern humans exist within an increasingly polluted environmental ecosystem involving pesticides, herbicides, microplastics, heavy metals, endocrine disruptors, persistent organic pollutants, industrial contaminants, and airborne toxicants.

These toxicological exposures may influence mitochondrial function, endocrine signaling, immune regulation, reproductive health, metabolic homeostasis, adaptive stress responses, and chronic inflammatory pathways[26,28,29,150,185].

Both plant and animal food systems may accumulate environmental toxicants depending on agricultural practices, industrial pollution, food processing, water quality, and bioaccumulation patterns. Consequently, reducing cumulative toxicological exposure becomes an important systems-level nutritional objective.

8.4. Low Toxin Burden

No modern food system is entirely toxin-free. Different dietary systems may shift toxicological exposure profiles rather than eliminate toxicity altogether.

Accordingly, systems nutrition should aim to reduce cumulative toxicological burden, oxidative stress load, inflammatory triggers, mitochondrial injury, and detoxification overload.

Potential toxicological contributors include pesticide residues, glyphosate, plant defense compounds, oxidized oils, advanced glycation end products, food additives, persistent organic pollutants, heavy metals, and endogenous metabolic toxins generated through chronic hyperglycemia and oxidative stress.

Within this framework, toxicological burden should be evaluated according to dose, duration, tissue accumulation, mitochondrial resilience, nutrient sufficiency, detoxification capacity, energetic adaptability, and individual susceptibility rather than simplistic “good food versus bad food” categorizations[96,179,192,198].

8.5. Nutrient Sufficiency

Optimal health requires more than caloric adequacy alone. Human physiology depends fundamentally upon adequate intake of water, vitamins, minerals, trace elements, amino acids, essential fatty acids, and mitochondrial cofactors.

Modern populations may simultaneously exhibit chronic dehydration, caloric excess, obesity, and micronutrient insufficiency. This paradox may partly result from widespread consumption of nutrient-poor ultra-processed foods.

From an IOM Systems Medicine perspective, nutrient sufficiency should emphasize nutrient density, bioavailability, mitochondrial and energetic support, orthomolecular adequacy, adaptive physiological demand, and the Nutrient Demand Principle[199], which proposes that physiological stress and chronic disease states may substantially increase micronutrient requirements[21,88,101,203].

Adequate nutrient status may also play important roles in maintaining mitochondrial energetics, oxidative-reduction balance, recovery capacity, metabolic adaptability, immune resilience, and long-term physiological stability.

8.6. Metabolic Flexibility

Metabolic flexibility refers to the capacity to efficiently transition between glucose metabolism, fatty acid oxidation, and ketone utilization according to physiological conditions.

Loss of metabolic flexibility may contribute to insulin resistance, obesity, mitochondrial dysfunction, fatigue, impaired stress resilience, reduced energetic adaptability, and chronic inflammatory activation.

 doi:10.20944/preprints202605.0616.v1

Nutritional strategies such as carbohydrate restriction, fasting, exercise, time-restricted feeding, and ketogenic therapies may help restore metabolic flexibility and mitochondrial adaptability in selected individuals[13,47,135,137].

Ketone bodies themselves may also function as signaling molecules influencing oxidative stress regulation, mitochondrial biogenesis, inflammatory signaling, and cellular stress resistance.

Restoration of metabolic flexibility may also improve adaptive fuel utilization during fasting, prolonged exertion, fluctuating nutrient availability, and other forms of physiological stress.

8.7. Energetic Resilience

Human physiology evolved under conditions characterized by fluctuating food availability, intermittent fasting, prolonged physical exertion, environmental stress, migration, and variable energy access. Accordingly, the capacity to maintain stable physiological function across changing energetic conditions may represent a fundamental feature of metabolic health.

From an IOM Systems Medicine perspective, energetic resilience refers to the ability to efficiently adapt between glucose metabolism, fatty acid oxidation, ketone utilization, and fluctuating energetic demands according to physiological stress and nutrient availability.

Loss of energetic resilience may contribute to chronic fatigue, impaired stress tolerance, metabolic inflexibility, mitochondrial dysfunction, reduced endurance capacity, diminished recovery capacity, and impaired physiological adaptability.

Nutritional strategies that support mitochondrial energetics, metabolic flexibility, nutrient sufficiency, circadian regulation, adaptive stress responses, and inflammatory balance may help preserve long-term energetic resilience and systems-level physiological stability.

8.8. Biological Compatibility

Ultimately, nutrition should support overall biological compatibility with human physiology.

From an IOM Systems Medicine perspective, optimal dietary systems should ideally support mitochondrial function, oxidative-reduction balance, hormonal regulation, immune tolerance, gut barrier integrity, vascular integrity, circadian biology, microbiome ecology, energetic resilience, and long-term physiological adaptability.

No single dietary pattern is likely optimal for all individuals under all conditions. Dietary responses may vary substantially according to genetics, microbiome composition, metabolic health, toxicological burden, life stage, endocrine status, physical activity, environmental exposures, and chronic disease burden.

Accordingly, systems nutrition emphasizes personalization, metabolic context, biological resilience, energetic adaptability, and dynamic physiological responsiveness rather than rigid ideological dietary prescriptions[4,86,150,200].

Within this framework, the ultimate goal of nutrition is not merely prevention of deficiency disease, but optimization of systems resilience, mitochondrial energetics, metabolic adaptability, energetic resilience, biological repair capacity, adaptive stress tolerance, and long-term human healthspan.

9. Conclusion

The central nutritional question of the 21st century may no longer be whether a diet is low-fat, plant-based, ketogenic, carnivorous, Mediterranean, vegan, or omnivorous, but whether it is biologically compatible with human physiology and capable of restoring systems-level resilience within the context of modern environmental and metabolic stressors.

Over the past century, nutritional science has often been dominated by reductionist frameworks emphasizing isolated variables such as calories, saturated fat, cholesterol, macronutrient ratios, or single nutrients. While such approaches have provided valuable mechanistic insights, they may insufficiently account for the broader systems-level interactions that govern human physiology.

 doi:10.20944/preprints202605.0616.v1

Chronic diseases including obesity, type 2 diabetes mellitus, atherosclerotic cardiovascular disease, neurodegenerative disorders, autoimmune disease, cancer, and metabolic syndrome are increasingly recognized as complex systems disorders involving dynamic interactions among metabolism, mitochondrial energetics, hormonal signaling, immune regulation, oxidative-reduction balance, environmental toxicology, microbiome ecology, vascular integrity, energetic adaptability, and nutrient availability.

Within this framework, nutrition should not be reduced to dietary ideology. Human diets should instead be evaluated according to their integrated effects on metabolism, mitochondrial function, inflammatory regulation, nutrient sufficiency, detoxification capacity, toxicological burden, endocrine signaling, microbiome integrity, vascular biology, energetic resilience, and overall biological resilience.

Importantly, no modern dietary system is entirely free of limitations or toxicological tradeoffs. Different dietary patterns may shift glycemic burden, nutrient density, inflammatory exposure, toxicological profiles, microbiome interactions, energetic demands, and metabolic stressors rather than completely eliminating physiological burden itself.

Consequently, the optimal nutritional framework may not consist of rigid adherence to any single dietary ideology, but rather minimization of cumulative metabolic and toxicological burden, optimization of nutrient sufficiency and bioavailability, preservation of metabolic flexibility and energetic resilience, reduction of ultra-processed food exposure, support of mitochondrial energetics, maintenance of gut and vascular barrier integrity, and enhancement of long-term physiological adaptability.

From an IOM Systems Medicine perspective, chronic disease may emerge when cumulative physiological burden exceeds the body's adaptive, energetic, and restorative capacity. Such burden may arise through interactions among hyperglycemia, chronic hyperinsulinemia, nutrient insufficiency, environmental toxicants, oxidative stress, mitochondrial dysfunction, endocrine disruption, chronic inflammation, microbiome dysregulation, impaired detoxification systems, and loss of metabolic flexibility.

Conversely, restoration of health may require systems-level interventions capable of simultaneously improving metabolic regulation, mitochondrial and energetic resilience, nutrient status, inflammatory balance, vascular integrity, adaptive stress tolerance, and detoxification reserve.

Within this paradigm, nutrition becomes not merely a source of calories, but a foundational biological signaling system influencing gene expression, mitochondrial bioenergetics, hormonal networks, immune tolerance, cellular repair, adaptive stress responses, and long-term healthspan trajectories.

Importantly, biological individuality must remain central to future nutritional science. Optimal dietary approaches may vary substantially according to genetics, microbiome composition, metabolic health, toxicological burden, physical activity, endocrine status, life stage, environmental exposures, energetic demands, and chronic disease state. Therefore, personalized systems-based nutrition may ultimately prove more biologically relevant than rigid universal dietary prescriptions.

The IOM Systems Nutrition Framework proposed in this paper emphasizes:

1. Low Glycemic Burden
2. Low Processing Burden
3. Low Pollution Burden
4. Low Toxicological Burden
5. Nutrient Sufficiency
6. Metabolic Flexibility

 doi:10.20944/preprints202605.0616.v1

7. Energetic Resilience

8. Biological Compatibility

Collectively, these principles seek to integrate nutritional biochemistry, metabolic physiology, toxicology, mitochondrial medicine, orthomolecular medicine, systems biology, evolutionary physiology, and chronic disease prevention into a unified systems-level framework.

A systems-level nutritional paradigm may therefore provide a more comprehensive foundation for prevention of chronic disease, restoration of metabolic resilience, preservation of vascular and mitochondrial integrity, optimization of human performance, enhancement of adaptive physiological capacity, and extension of long-term healthspan in the modern era.

The capacity to maintain energetic adaptability across fluctuating nutritional and environmental conditions may represent a central but underappreciated determinant of long-term human physiological resilience.

Future research should increasingly move beyond polarized dietary ideologies toward integrative investigation of how nutrition interacts dynamically with metabolism, environmental toxicology, mitochondrial biology, immune regulation, microbiome ecology, adaptive energetics, and systems-level human physiology.

Such an approach may help establish a more biologically coherent nutritional model for 21st century medicine and public health.

The integrated principles of the proposed IOM Systems Nutrition Framework are summarized in Figure 3.

Top of Form

Bottom of Form

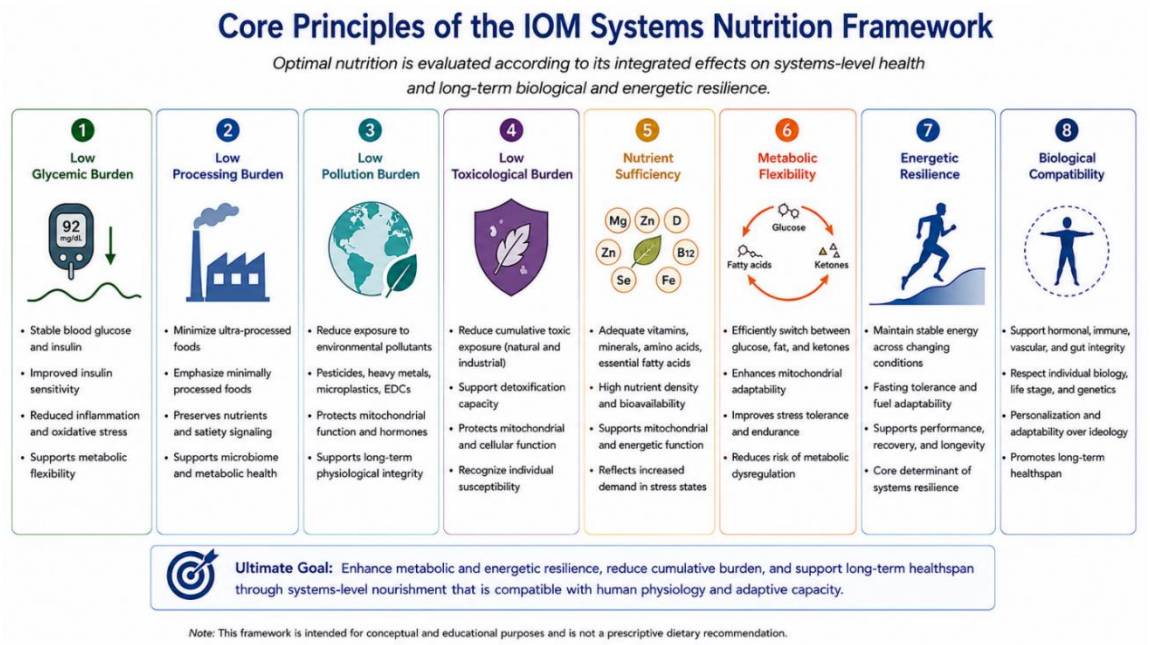

Figure 3. ***Core Principles of the IOM Systems Nutrition Framework***. The proposed IOM Systems Nutrition Framework emphasizes evaluation of dietary systems according to their integrated effects on systems-level physiology, metabolic resilience, mitochondrial energetics, and long-term biological adaptability. The framework includes eight interconnected principles: (1) Low Glycemic Burden, emphasizing reduction of chronic hyperglycemia and hyperinsulinemia; (2) Low Processing Burden, emphasizing minimization of ultra-processed foods; (3) Low Pollution Burden, emphasizing reduction of environmental toxicological exposure; (4) Low Toxicological Burden, emphasizing cumulative reduction of dietary and endogenous toxicological stress;

 doi:10.20944/preprints202605.0616.v1

(5) Nutrient Sufficiency, emphasizing nutrient density, bioavailability, and orthomolecular support; (6) Metabolic Flexibility, referring to adaptive fuel switching between glucose, fatty acids, and ketone metabolism; (7) Energetic Resilience, referring to maintenance of physiological stability across changing energetic and environmental conditions; and (8) Biological Compatibility, emphasizing individualized physiological adaptability and systems integrity. Collectively, these principles are proposed as a systems-level framework for evaluating dietary compatibility with human physiology and long-term healthspan.

This paper is intended primarily as a conceptual and systems-level synthesis integrating evolutionary physiology, nutritional science, metabolic biology, toxicology, and Integrative Orthomolecular Medicine (IOM) principles. Many concepts discussed remain areas of active investigation, and some proposed mechanisms require further validation through long-term clinical trials, mechanistic studies, and systems-biology research. Dietary responses are highly individualized and influenced by genetics, microbiome composition, metabolic health, environmental exposures, lifestyle factors, and physiological context. Accordingly, the framework proposed should be interpreted as a comparative systems-level model rather than a universal dietary prescription.

Declarations

Competing Interests: Richard Z. Cheng, M.D., Ph.D., serves as a Board Director of the Riordan Clinic, an institution involved in research and clinical applications related to intravenous vitamin C and orthomolecular medicine. The present manuscript is a conceptual, systems-based, and literature-derived analysis and does not report proprietary data, commercial interventions, sponsored research, or patient-level clinical trial outcomes. No financial compensation or external commercial support was received for the preparation of this manuscript.

Funding: This work received no external funding.

Ethics Approval and Consent to Participate: Not applicable. This manuscript is a conceptual synthesis and analysis of previously published literature and does not involve new human participants, animal experiments, or identifiable patient data.

Consent for Publication: Not applicable.

Data Availability: No new datasets were generated or analyzed during the preparation of this manuscript. All information discussed is derived from previously published and publicly available sources cited within the manuscript.

Author Contributions: R.Z.C. conceived the conceptual framework, performed the literature review and systems-level synthesis, developed the figures and comparative models, and wrote and revised the manuscript.

References

1. Noncommunicable Diseases. Available online: https://www.who.int/health-topics/noncommunicable-diseases (accessed 7 May 2026).
2. Ng, M.; Dai, X.; Cogen, R.M.; et al. National-Level and State-Level Prevalence of Overweight and Obesity among Children, Adolescents, and Adults in the USA, 1990–2021, and Forecasts up to 2050. *The Lancet* 2024, *404*, (10469), 2278–2298. DOI: 10.1016/S0140-6736(24)01548-4; Available online: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01548-4/fulltext?utm_source=chatgpt.com.

 doi:10.20944/preprints202605.0616.v1

3. IDF Diabetes Atlas 10th Edition 2021. Available online: https://idf.org/about-diabetes/resources/idf-diabetes-atlas-2021/ (accessed 7 May 2026).
4. Hotamisligil, G.S. Inflammation and Metabolic Disorders. *Nature* 2006, *444*, (7121), 860–867. DOI: 10.1038/nature05485.
5. Defronzo, R.A. Banting Lecture. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes* 2009, *58*, (4), 773–795. DOI: 10.2337/db09-9028.
6. Fabbri, E.; Zoli, M.; Gonzalez-Freire, M.; et al. Aging and Multimorbidity: New Tasks, Priorities, and Frontiers for Integrated Gerontological and Clinical Research. *J Am Med Dir Assoc* 2015, *16*, (8), 640–647. DOI: 10.1016/j.jamda.2015.03.013.
7. Franceschi, C.; Garagnani, P.; Parini, P.; et al. Inflammaging: A New Immune-Metabolic Viewpoint for Age-Related Diseases. *Nat Rev Endocrinol* 2018, *14*, (10), 576–590. DOI: 10.1038/s41574-018-0059-4.
8. Hanahan, D. Hallmarks of Cancer: New Dimensions. *Cancer Discov* 2022, *12*, (1), 31–46. DOI: 10.1158/2159-8290.CD-21-1059.
9. Lynch, S.V.; Pedersen, O. The Human Intestinal Microbiome in Health and Disease. *New England Journal of Medicine* 2016, *375*, (24), 2369–2379. DOI: 10.1056/NEJMra1600266; Available online: https://www.nejm.org/doi/full/10.1056/NEJMra1600266.
10. Fasano, A. Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer. *Physiol Rev* 2011, *91*, (1), 151–175. DOI: 10.1152/physrev.00003.2008.
11. Wallace, D.C. Mitochondrial Diseases in Man and Mouse. *Science* 1999, *283*, (5407), 1482–1488. DOI: 10.1126/science.283.5407.1482.
12. Xu, X.; Pang, Y.; Fan, X. Mitochondria in Oxidative Stress, Inflammation and Aging: From Mechanisms to Therapeutic Advances. *Sig Transduct Target Ther* 2025, *10*, (1), 190. DOI: 10.1038/s41392-025-02253-4; Available online: https://www.nature.com/articles/s41392-025-02253-4.
13. Veech, R.L. The Therapeutic Implications of Ketone Bodies: The Effects of Ketone Bodies in Pathological Conditions: Ketosis, Ketogenic Diet, Redox States, Insulin Resistance, and Mitochondrial Metabolism. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2004, *70*, (3), 309–319. DOI: 10.1016/j.plefa.2003.09.007; Available online: https://www.sciencedirect.com/science/article/pii/S0952327803002217.
14. Goodpaster, B.H.; Sparks, L.M. Metabolic Flexibility in Health and Disease. *Cell Metab* 2017, *25*, (5), 1027–1036. DOI: 10.1016/j.cmet.2017.04.015.
15. Czech, M.P. Insulin Action and Resistance in Obesity and Type 2 Diabetes. *Nat Med* 2017, *23*, (7), 804–814. DOI: 10.1038/nm.4350.
16. Vaidya, R.A.; Desai, S.; Moitra, P.; et al. Hyperinsulinemia: An Early Biomarker of Metabolic Dysfunction. *Front Clin Diabetes Healthc* 2023, *4*, 1159664. DOI: 10.3389/fcdhc.2023.1159664.

 doi:10.20944/preprints202605.0616.v1

17. Furman, D.; Campisi, J.; Verdin, E.; et al. Chronic Inflammation in the Etiology of Disease across the Life Span. *Nat Med* 2019, *25*, (12), 1822–1832. DOI: 10.1038/s41591-019-0675-0.
18. Sies, H. Oxidative Stress: A Concept in Redox Biology and Medicine. *Redox Biol* 2015, *4*, 180–183. DOI: 10.1016/j.redox.2015.01.002.
19. Jones, D.P.; Sies, H. The Redox Code. *Antioxid Redox Signal* 2015, *23*, (9), 734–746. DOI: 10.1089/ars.2015.6247.
20. Fishbein, A.B.; Knutson, K.L.; Zee, P.C. Circadian Disruption and Human Health. *J Clin Invest* 2021, *131*, (19), e148286. DOI: 10.1172/JCI148286.
21. Ames, B.N. Low Micronutrient Intake May Accelerate the Degenerative Diseases of Aging through Allocation of Scarce Micronutrients by Triage. *Proc Natl Acad Sci U S A* 2006, *103*, (47), 17589–17594. DOI: 10.1073/pnas.0608757103.
22. Monteiro, C.A.; Cannon, G.; Levy, R.B.; et al. Ultra-Processed Foods: What They Are and How to Identify Them. *Public Health Nutr* 2019, *22*, (5), 936–941. DOI: 10.1017/S1368980018003762.
23. Hall, K.D.; Ayuketah, A.; Brychta, R.; et al. Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of Ad Libitum Food Intake. *Cell Metab* 2019, *30*, (1), 67-77.e3. DOI: 10.1016/j.cmet.2019.05.008.
24. Srour, B.; Fezeu, L.K.; Kesse-Guyot, E.; et al. Ultra-Processed Food Intake and Risk of Cardiovascular Disease: Prospective Cohort Study (NutriNet-Santé). *BMJ* 2019, *365*, l1451. DOI: 10.1136/bmj.l1451.
25. Fang, Z.; Rossato, S.L.; Hang, D.; et al. Association of Ultra-Processed Food Consumption with All Cause and Cause Specific Mortality: Population Based Cohort Study. *BMJ* 2024, *385*, e078476. DOI: 10.1136/bmj-2023-078476.
26. Fuller, R.; Landrigan, P.J.; Balakrishnan, K.; et al. Pollution and Health: A Progress Update. *Lancet Planet Health* 2022, *6*, (6), e535–e547. DOI: 10.1016/S2542-5196(22)00090-0.
27. Peralta, M.; Lizcano, F. Endocrine Disruptors and Metabolic Changes: Impact on Puberty Control. *Endocrine Practice* 2024, *30*, (4), 384–397. DOI: 10.1016/j.eprac.2024.01.006; Available online: https://www.endocrinepractice.org/article/S1530-891X%2824%2900038-7/abstract?utm_source=chatgpt.com.
28. Vandenberg, L.N.; Colborn, T.; Hayes, T.B.; et al. Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. *Endocr Rev* 2012, *33*, (3), 378–455. DOI: 10.1210/er.2011-1050.
29. Leslie, H.A.; Velzen, M.J.M. van; Brandsma, S.H.; et al. Discovery and Quantification of Plastic Particle Pollution in Human Blood. *Environ Int* 2022, *163*, 107199. DOI: 10.1016/j.envint.2022.107199.
30. Beretta, M.V.; Flores, C.A.O.; Colameo, G.F.; et al. Low-Carbohydrate Dietary Interventions for Metabolic Control in Individuals With Type 2 Diabetes Mellitus: An Overview of Systematic Reviews. *Nutr Rev* 2025, *83*, (7), e1677–e1692. DOI: 10.1093/nutrit/nuae123.

 doi:10.20944/preprints202605.0616.v1

31. Feinman, R.D.; Pogozelski, W.K.; Astrup, A.; et al. Dietary Carbohydrate Restriction as the First Approach in Diabetes Management: Critical Review and Evidence Base. *Nutrition* 2015, *31*, (1), 1–13. DOI: 10.1016/j.nut.2014.06.011.
32. McKenzie, A.L.; Athinarayanan, S.J.; Van Tieghem, M.R.; et al. 5-Year Effects of a Novel Continuous Remote Care Model with Carbohydrate-Restricted Nutrition Therapy Including Nutritional Ketosis in Type 2 Diabetes: An Extension Study. *Diabetes Res Clin Pract* 2024, *217*, 111898. DOI: 10.1016/j.diabres.2024.111898.
33. Westman, E.C.; Feinman, R.D.; Mavropoulos, J.C.; et al. Low-Carbohydrate Nutrition and Metabolism. *Am J Clin Nutr* 2007, *86*, (2), 276–284. DOI: 10.1093/ajcn/86.2.276.
34. Seyfried, T.N. *Cancer as a Metabolic Disease: On the Origin, Management, and Prevention of Cancer*; Wiley, 2012.; Available online: https://www.wiley.com/en-us/Cancer+as+a+Metabolic+Disease%3A+On+the+Origin%2C+Management%2C+and+Prevention+of+Cancer-p-9780470584927.
35. Wolfe, R.R.; Miller, S.L.; Miller, K.B. Optimal Protein Intake in the Elderly. *Clin Nutr* 2008, *27*, (5), 675–684. DOI: 10.1016/j.clnu.2008.06.008.
36. Vliet, S. van; Bain, J.R.; Muehlbauer, M.J.; et al. A Metabolomics Comparison of Plant-Based Meat and Grass-Fed Meat Indicates Large Nutritional Differences despite Comparable Nutrition Facts Panels. *Sci Rep* 2021, *11*, (1), 13828. DOI: 10.1038/s41598-021-93100-3; Available online: https://www.nature.com/articles/s41598-021-93100-3.
37. Shaghaghian, S.; McClements, D.J.; Khalesi, M.; et al. Digestibility and Bioavailability of Plant-Based Proteins Intended for Use in Meat Analogues: A Review. *Trends in Food Science & Technology* 2022, *129*, 646–656. DOI: 10.1016/j.tifs.2022.11.016; Available online: https://www.sciencedirect.com/science/article/pii/S0924224422004526.
38. Cordain, L.; Miller, J.B.; Eaton, S.B.; et al. Plant-Animal Subsistence Ratios and Macronutrient Energy Estimations in Worldwide Hunter-Gatherer Diets. *Am J Clin Nutr* 2000, *71*, (3), 682–692. DOI: 10.1093/ajcn/71.3.682.
39. Noakes, T.D.; Windt, J. Evidence That Supports the Prescription of Low-Carbohydrate High-Fat Diets: A Narrative Review. *Br J Sports Med* 2017, *51*, (2), 133–139. DOI: 10.1136/bjsports-2016-096491.
40. Chai, W.; Liebman, M. Effect of Different Cooking Methods on Vegetable Oxalate Content. *J Agric Food Chem* 2005, *53*, (8), 3027–3030. DOI: 10.1021/jf048128d.
41. Pontzer, H. Energy Expenditure in Humans and Other Primates: A New Synthesis*. *Annual Review of Anthropology* 2015, *44*, (Volume 44, 2015), 169–187. DOI: 10.1146/annurev-anthro-102214-013925; Available online: https://www.annualreviews.org/content/journals/10.1146/annurev-anthro-102214-013925.

 doi:10.20944/preprints202605.0616.v1

42. Leonard, W.R.; Robertson, M.L. Evolutionary Perspectives on Human Nutrition: The Influence of Brain and Body Size on Diet and Metabolism. *Am J Hum Biol* 1994, *6*, (1), 77–88. DOI: 10.1002/ajhb.1310060111.
43. Eaton, S.B.; Eaton, S.B.; Konner, M.J. Paleolithic Nutrition Revisited: A Twelve-Year Retrospective on Its Nature and Implications. *Eur J Clin Nutr* 1997, *51*, (4), 207–216. DOI: 10.1038/sj.ejcn.1600389.
44. Cordain, L.; Eaton, S.B.; Sebastian, A.; et al. Origins and Evolution of the Western Diet: Health Implications for the 21st Century. *Am J Clin Nutr* 2005, *81*, (2), 341–354. DOI: 10.1093/ajcn.81.2.341.
45. Cahill, G.F. Fuel Metabolism in Starvation. *Annu Rev Nutr* 2006, *26*, 1–22. DOI: 10.1146/annurev.nutr.26.061505.111258.
46. Owen, O.E.; Morgan, A.P.; Kemp, H.G.; et al. Brain Metabolism during Fasting. *J Clin Invest* 1967, *46*, (10), 1589–1595. DOI: 10.1172/JCI105650; Available online: https://www.jci.org/articles/view/105650.
47. Newman, J.C.; Verdin, E. Ketone Bodies as Signaling Metabolites. *Trends Endocrinol Metab* 2014, *25*, (1), 42–52. DOI: 10.1016/j.tem.2013.09.002.
48. Kelley, D.E.; Mandarino, L.J. Fuel Selection in Human Skeletal Muscle in Insulin Resistance: A Reexamination. *Diabetes* 2000, *49*, (5), 677–683. DOI: 10.2337/diabetes.49.5.677.
49. Milton, K. The Critical Role Played by Animal Source Foods in Human (Homo) Evolution. *J Nutr* 2003, *133*, (11 Suppl 2), 3886S-3892S. DOI: 10.1093/jn/133.11.3886S.
50. Ungar, P.S.; Sponheimer, M. The Diets of Early Hominins. *Science* 2011, *334*, (6053), 190–193. DOI: 10.1126/science.1207701.
51. Richards, M.P.; Pettitt, P.B.; Trinkaus, E.; et al. Neanderthal Diet at Vindija and Neanderthal Predation: The Evidence from Stable Isotopes. *Proc Natl Acad Sci U S A* 2000, *97*, (13), 7663–7666. DOI: 10.1073/pnas.120178997.
52. Henry, A.G.; Brooks, A.S.; Piperno, D.R. Microfossils in Calculus Demonstrate Consumption of Plants and Cooked Foods in Neanderthal Diets (Shanidar III, Iraq; Spy I and II, Belgium). *Proceedings of the National Academy of Sciences* 2011, *108*, (2), 486–491. DOI: 10.1073/pnas.1016868108; Available online: https://www.pnas.org/doi/10.1073/pnas.1016868108.
53. Ben-Dor, M.; Sirtoli, R.; Barkai, R. The Evolution of the Human Trophic Level during the Pleistocene. *Am J Phys Anthropol* 2021, *175 Suppl 72*, 27–56. DOI: 10.1002/ajpa.24247.
54. Pontzer, H.; Raichlen, D.A.; Wood, B.M.; et al. Hunter-Gatherer Energetics and Human Obesity. *PLOS ONE* 2012, *7*, (7), e40503. DOI: 10.1371/journal.pone.0040503; Available online: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0040503.
55. Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids 2005 National Academies of Sciences, Engineering, and Medicine. 2005. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids.*; 2005.

 doi:10.20944/preprints202605.0616.v1

DOI: https://doi.org/10.17226/10490; Available online: https://www.nationalacademies.org/read/10490/chapter/12.

56. DiNicolantonio, J.J.; O'Keefe, J.H. Omega-6 Vegetable Oils as a Driver of Coronary Heart Disease: The Oxidized Linoleic Acid Hypothesis. *Open Heart* 2018, *5*, (2), e000898. DOI: 10.1136/openhrt-2018-000898; Available online: https://pmc.ncbi.nlm.nih.gov/articles/PMC6196963/.
57. GBD 2021 Adult BMI Collaborators Global, Regional, and National Prevalence of Adult Overweight and Obesity, 1990-2021, with Forecasts to 2050: A Forecasting Study for the Global Burden of Disease Study 2021. *Lancet* 2025, *405*, (10481), 813–838. DOI: 10.1016/S0140-6736(25)00355-1.
58. Ludwig, D.S.; Ebbeling, C.B. The Carbohydrate-Insulin Model of Obesity: Beyond "Calories In, Calories Out." *JAMA Intern Med* 2018, *178*, (8), 1098–1103. DOI: 10.1001/jamainternmed.2018.2933.
59. Hall, K.D.; Guo, J. Obesity Energetics: Body Weight Regulation and the Effects of Diet Composition. *Gastroenterology* 2017, *152*, (7), 1718-1727.e3. DOI: 10.1053/j.gastro.2017.01.052.
60. Longo, V.D.; Panda, S. Fasting, Circadian Rhythms, and Time-Restricted Feeding in Healthy Lifespan. *Cell Metab* 2016, *23*, (6), 1048–1059. DOI: 10.1016/j.cmet.2016.06.001.
61. Mattson, M.P.; Moehl, K.; Ghena, N.; et al. Intermittent Metabolic Switching, Neuroplasticity and Brain Health. *Nat Rev Neurosci* 2018, *19*, (2), 63–80. DOI: 10.1038/nrn.2017.156.
62. Paoli, A.; Rubini, A.; Volek, J.S.; et al. Beyond Weight Loss: A Review of the Therapeutic Uses of Very-Low-Carbohydrate (Ketogenic) Diets. *Eur J Clin Nutr* 2013, *67*, (8), 789–796. DOI: 10.1038/ejcn.2013.116; Available online: https://www.nature.com/articles/ejcn2013116.
63. Gerich, J.E. Control of Glycaemia. *Baillieres Clin Endocrinol Metab* 1993, *7*, (3), 551–586. DOI: 10.1016/s0950-351x(05)80207-1.
64. Consoli, A. Role of Liver in Pathophysiology of NIDDM. *Diabetes Care* 1992, *15*, (3), 430–441. DOI: 10.2337/diacare.15.3.430.
65. Cahill, G.F. Starvation in Man. *N Engl J Med* 1970, *282*, (12), 668–675. DOI: 10.1056/NEJM197003192821209.
66. Cunnane, S.C.; Courchesne-Loyer, A.; Vandenberghe, C.; et al. Can Ketones Help Rescue Brain Fuel Supply in Later Life? Implications for Cognitive Health during Aging and the Treatment of Alzheimer's Disease. *Front Mol Neurosci* 2016, *9*, 53. DOI: 10.3389/fnmol.2016.00053.
67. Kashiwaya, Y.; Takeshima, T.; Mori, N.; et al. D-Beta-Hydroxybutyrate Protects Neurons in Models of Alzheimer's and Parkinson's Disease. *Proc Natl Acad Sci U S A* 2000, *97*, (10), 5440–5444. DOI: 10.1073/pnas.97.10.5440.
68. Samuel, V.T.; Shulman, G.I. Mechanisms for Insulin Resistance: Common Threads and Missing Links. *Cell* 2012, *148*, (5), 852–871. DOI: 10.1016/j.cell.2012.02.017.

 doi:10.20944/preprints202605.0616.v1

69. Blasbalg, T.L.; Hibbeln, J.R.; Ramsden, C.E.; et al. Changes in Consumption of Omega-3 and Omega-6 Fatty Acids in the United States during the 20th Century. *Am J Clin Nutr* 2011, *93*, (5), 950–962. DOI: 10.3945/ajcn.110.006643.
70. Muoio, D.M. Metabolic Inflexibility: When Mitochondrial Indecision Leads to Metabolic Gridlock. *Cell* 2014, *159*, (6), 1253–1262. DOI: 10.1016/j.cell.2014.11.034.
71. Eaton, S.B.; Konner, M. Paleolithic Nutrition. A Consideration of Its Nature and Current Implications. *N Engl J Med* 1985, *312*, (5), 283–289. DOI: 10.1056/NEJM198501313120505.
72. Smith, R.L.; Soeters, M.R.; Wüst, R.C.I.; et al. Metabolic Flexibility as an Adaptation to Energy Resources and Requirements in Health and Disease. *Endocr Rev* 2018, *39*, (4), 489–517. DOI: 10.1210/er.2017-00211.
73. Cahill, G.F.; Owen, O.E. Starvation and Survival. *Trans Am Clin Climatol Assoc* 1968, *79*, 13–20.
74. Newman, J.C.; Verdin, E. β-Hydroxybutyrate: Much More than a Metabolite. *Diabetes Res Clin Pract* 2014, *106*, (2), 173–181. DOI: 10.1016/j.diabres.2014.08.009.
75. Kelley, D.E.; Goodpaster, B.H. Skeletal Muscle Triglyceride. An Aspect of Regional Adiposity and Insulin Resistance. *Diabetes Care* 2001, *24*, (5), 933–941. DOI: 10.2337/diacare.24.5.933.
76. Galgani, J.E.; Moro, C.; Ravussin, E. Metabolic Flexibility and Insulin Resistance. *Am J Physiol Endocrinol Metab* 2008, *295*, (5), E1009-1017. DOI: 10.1152/ajpendo.90558.2008.
77. Storlien, L.; Oakes, N.D.; Kelley, D.E. Metabolic Flexibility. *Proc Nutr Soc* 2004, *63*, (2), 363–368. DOI: 10.1079/PNS2004349.
78. Phinney, S.D.; Bistrian, B.R.; Evans, W.J.; et al. The Human Metabolic Response to Chronic Ketosis without Caloric Restriction: Preservation of Submaximal Exercise Capability with Reduced Carbohydrate Oxidation. *Metabolism* 1983, *32*, (8), 769–776. DOI: 10.1016/0026-0495(83)90106-3.
79. Volek, J.S.; Freidenreich, D.J.; Saenz, C.; et al. Metabolic Characteristics of Keto-Adapted Ultra-Endurance Runners. *Metabolism* 2016, *65*, (3), 100–110. DOI: 10.1016/j.metabol.2015.10.028.
80. Noakes, T.D.; Prins, P.J.; Volek, J.S.; et al. Low Carbohydrate High Fat Ketogenic Diets on the Exercise Crossover Point and Glucose Homeostasis. *Front Physiol* 2023, *14*, 1150265. DOI: 10.3389/fphys.2023.1150265.
81. Panda, S. Circadian Physiology of Metabolism. *Science* 2016, *354*, (6315), 1008–1015. DOI: 10.1126/science.aah4967.
82. Chaix, A.; Zarrinpar, A.; Miu, P.; et al. Time-Restricted Feeding Is a Preventative and Therapeutic Intervention against Diverse Nutritional Challenges. *Cell Metab* 2014, *20*, (6), 991–1005. DOI: 10.1016/j.cmet.2014.11.001.
83. Drewnowski, A. Concept of a Nutritious Food: Toward a Nutrient Density Score. *Am J Clin Nutr* 2005, *82*, (4), 721–732. DOI: 10.1093/ajcn/82.4.721.

 doi:10.20944/preprints202605.0616.v1

84. Fardet, A. Minimally Processed Foods Are More Satiating and Less Hyperglycemic than Ultra-Processed Foods: A Preliminary Study with 98 Ready-to-Eat Foods. *Food Funct* 2016, *7*, (5), 2338–2346. DOI: 10.1039/c6fo00107f.
85. Mozaffarian, D. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review. *Circulation* 2016, *133*, (2), 187–225. DOI: 10.1161/CIRCULATIONAHA.115.018585.
86. Popkin, B.M.; Adair, L.S.; Ng, S.W. Global Nutrition Transition and the Pandemic of Obesity in Developing Countries. *Nutr Rev* 2012, *70*, (1), 3–21. DOI: 10.1111/j.1753-4887.2011.00456.x.
87. Matthews, J.J.; Arentson-Lantz, E.J.; Moughan, P.J.; et al. Understanding Dietary Protein Quality: Digestible Indispensable Amino Acid Scores and Beyond. *The Journal of Nutrition* 2025, *155*, (10), 3152–3167. DOI: 10.1016/j.tjnut.2025.07.005; Available online: https://www.sciencedirect.com/science/article/pii/S0022316625004286.
88. *Dietary Protein Quality Evaluation in Human Nutrition: Report of an FAO Expert Consultation, 31 March-2 April, 2011, Auckland, New Zealand*; Food and Agriculture Organization of the United Nations, Rome, 2013.
89. Wolfe, R.R. Branched-Chain Amino Acids and Muscle Protein Synthesis in Humans: Myth or Reality? *J Int Soc Sports Nutr* 2017, *14*, 30. DOI: 10.1186/s12970-017-0184-9.
90. Fardet, A.; Rock, E. Toward a New Philosophy of Preventive Nutrition: From a Reductionist to a Holistic Paradigm to Improve Nutritional Recommendations. *Adv Nutr* 2014, *5*, (4), 430–446. DOI: 10.3945/an.114.006122.
91. Lustig, R.H. Ultraprocessed Food: Addictive, Toxic, and Ready for Regulation. *Nutrients* 2020, *12*, (11), 3401. DOI: 10.3390/nu12113401.
92. Popkin, B.M.; Corvalan, C.; Grummer-Strawn, L.M. Dynamics of the Double Burden of Malnutrition and the Changing Nutrition Reality. *Lancet* 2020, *395*, (10217), 65–74. DOI: 10.1016/S0140-6736(19)32497-3.
93. Pagliai, G.; Dinu, M.; Madarena, M.P.; et al. Consumption of Ultra-Processed Foods and Health Status: A Systematic Review and Meta-Analysis. *Br J Nutr* 2021, *125*, (3), 308–318. DOI: 10.1017/S0007114520002688.
94. Lane, M.M.; Gamage, E.; Du, S.; et al. Ultra-Processed Food Exposure and Adverse Health Outcomes: Umbrella Review of Epidemiological Meta-Analyses. *BMJ* 2024, *384*, e077310. DOI: 10.1136/bmj-2023-077310.
95. Taylor, R. Type 2 Diabetes: Etiology and Reversibility. *Diabetes Care* 2013, *36*, (4), 1047–1055. DOI: 10.2337/dc12-1805.
96. Brownlee, M. The Pathobiology of Diabetic Complications: A Unifying Mechanism. *Diabetes* 2005, *54*, (6), 1615–1625. DOI: 10.2337/diabetes.54.6.1615.
97. Simopoulos, A.P. The Importance of the Omega-6/Omega-3 Fatty Acid Ratio in Cardiovascular Disease and Other Chronic Diseases. *Exp Biol Med (Maywood)* 2008, *233*, (6), 674–688. DOI: 10.3181/0711-MR-311.

 doi:10.20944/preprints202605.0616.v1

98. Patterson, E.; Wall, R.; Fitzgerald, G.F.; et al. Health Implications of High Dietary Omega-6 Polyunsaturated Fatty Acids. *J Nutr Metab* 2012, *2012*, 539426. DOI: 10.1155/2012/539426.
99. Abete, I.; Astrup, A.; Martínez, J.A.; et al. Obesity and the Metabolic Syndrome: Role of Different Dietary Macronutrient Distribution Patterns and Specific Nutritional Components on Weight Loss and Maintenance. *Nutr Rev* 2010, *68*, (4), 214–231. DOI: 10.1111/j.1753-4887.2010.00280.x.
100. Troesch, B.; Biesalski, H.K.; Bos, R.; et al. Increased Intake of Foods with High Nutrient Density Can Help to Break the Intergenerational Cycle of Malnutrition and Obesity. *Nutrients* 2015, *7*, (7), 6016–6037. DOI: 10.3390/nu7075266.
101. Troesch, B.; Hoeft, B.; McBurney, M.; et al. Dietary Surveys Indicate Vitamin Intakes below Recommendations Are Common in Representative Western Countries. *Br J Nutr* 2012, *108*, (4), 692–698. DOI: 10.1017/S0007114512001808.
102. Passarelli, S.; Free, C.M.; Shepon, A.; et al. Global Estimation of Dietary Micronutrient Inadequacies: A Modelling Analysis. *Lancet Glob Health* 2024, *12*, (10), e1590–e1599. DOI: 10.1016/S2214-109X(24)00276-6.
103. Muscogiuri, G.; Barrea, L.; Laudisio, D.; et al. The Management of Very Low-Calorie Ketogenic Diet in Obesity Outpatient Clinic: A Practical Guide. *J Transl Med* 2019, *17*, (1), 356. DOI: 10.1186/s12967-019-2104-z.
104. Sofi, F.; Cesari, F.; Abbate, R.; et al. Adherence to Mediterranean Diet and Health Status: Meta-Analysis. *BMJ* 2008, *337*, a1344. DOI: 10.1136/bmj.a1344.
105. Estruch, R.; Ros, E.; Salas-Salvadó, J.; et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med* 2018, *378*, (25), e34. DOI: 10.1056/NEJMoa1800389.
106. Rosato, V.; Temple, N.J.; La Vecchia, C.; et al. Mediterranean Diet and Cardiovascular Disease: A Systematic Review and Meta-Analysis of Observational Studies. *Eur J Nutr* 2019, *58*, (1), 173–191. DOI: 10.1007/s00394-017-1582-0.
107. Dinu, M.; Pagliai, G.; Casini, A.; et al. Mediterranean Diet and Multiple Health Outcomes: An Umbrella Review of Meta-Analyses of Observational Studies and Randomised Trials. *Eur J Clin Nutr* 2018, *72*, (1), 30–43. DOI: 10.1038/ejcn.2017.58.
108. Martínez-González, M.A.; Gea, A.; Ruiz-Canela, M. The Mediterranean Diet and Cardiovascular Health. *Circ Res* 2019, *124*, (5), 779–798. DOI: 10.1161/CIRCRESAHA.118.313348.
109. Esposito, K.; Marfella, R.; Ciotola, M.; et al. Effect of a Mediterranean-Style Diet on Endothelial Dysfunction and Markers of Vascular Inflammation in the Metabolic Syndrome: A Randomized Trial. *JAMA* 2004, *292*, (12), 1440–1446. DOI: 10.1001/jama.292.12.1440.
110. Schwingshackl, L.; Lampousi, A.-M.; Portillo, M.P.; et al. Olive Oil in the Prevention and Management of Type 2 Diabetes Mellitus: A Systematic

 doi:10.20944/preprints202605.0616.v1

Review and Meta-Analysis of Cohort Studies and Intervention Trials. *Nutr Diabetes* 2017, *7*, (4), e262. DOI: 10.1038/nutd.2017.12.

111. Guasch-Ferré, M.; Li, Y.; Willett, W.C.; et al. Consumption of Olive Oil and Risk of Total and Cause-Specific Mortality Among U.S. Adults. *J Am Coll Cardiol* 2022, *79*, (2), 101–112. DOI: 10.1016/j.jacc.2021.10.041.
112. Covas, M.-I. Olive Oil and the Cardiovascular System. *Pharmacol Res* 2007, *55*, (3), 175–186. DOI: 10.1016/j.phrs.2007.01.010.
113. Ajala, O.; English, P.; Pinkney, J. Systematic Review and Meta-Analysis of Different Dietary Approaches to the Management of Type 2 Diabetes. *Am J Clin Nutr* 2013, *97*, (3), 505–516. DOI: 10.3945/ajcn.112.042457.
114. Tay, J.; Luscombe-Marsh, N.D.; Thompson, C.H.; et al. Comparison of Low- and High-Carbohydrate Diets for Type 2 Diabetes Management: A Randomized Trial. *Am J Clin Nutr* 2015, *102*, (4), 780–790. DOI: 10.3945/ajcn.115.112581.
115. Shai, I.; Schwarzfuchs, D.; Henkin, Y.; et al. Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet. *N Engl J Med* 2008, *359*, (3), 229–241. DOI: 10.1056/NEJMoa0708681.
116. Athinarayanan, S.J.; Adams, R.N.; Hallberg, S.J.; et al. Long-Term Effects of a Novel Continuous Remote Care Intervention Including Nutritional Ketosis for the Management of Type 2 Diabetes: A 2-Year Non-Randomized Clinical Trial. *Front Endocrinol (Lausanne)* 2019, *10*, 348. DOI: 10.3389/fendo.2019.00348.
117. Brehm, B.J.; Seeley, R.J.; Daniels, S.R.; et al. A Randomized Trial Comparing a Very Low Carbohydrate Diet and a Calorie-Restricted Low Fat Diet on Body Weight and Cardiovascular Risk Factors in Healthy Women. *J Clin Endocrinol Metab* 2003, *88*, (4), 1617–1623. DOI: 10.1210/jc.2002-021480.
118. Craig, W.J. Nutrition Concerns and Health Effects of Vegetarian Diets. *Nutr Clin Pract* 2010, *25*, (6), 613–620. DOI: 10.1177/0884533610385707.
119. Satija, A.; Bhupathiraju, S.N.; Rimm, E.B.; et al. Plant-Based Dietary Patterns and Incidence of Type 2 Diabetes in US Men and Women: Results from Three Prospective Cohort Studies. *PLoS Med* 2016, *13*, (6), e1002039. DOI: 10.1371/journal.pmed.1002039.
120. Tuso, P.J.; Ismail, M.H.; Ha, B.P.; et al. Nutritional Update for Physicians: Plant-Based Diets. *Perm J* 2013, *17*, (2), 61–66. DOI: 10.7812/TPP/12-085.
121. Yokoyama, Y.; Barnard, N.D.; Levin, S.M.; et al. Vegetarian Diets and Glycemic Control in Diabetes: A Systematic Review and Meta-Analysis. *Cardiovasc Diagn Ther* 2014, *4*, (5), 373–382. DOI: 10.3978/j.issn.2223-3652.2014.10.04.
122. Glenn, A.J.; Viguiliouk, E.; Seider, M.; et al. Relation of Vegetarian Dietary Patterns With Major Cardiovascular Outcomes: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Front Nutr* 2019, *6*, 80. DOI: 10.3389/fnut.2019.00080.
123. Satija, A.; Hu, F.B. Plant-Based Diets and Cardiovascular Health. *Trends Cardiovasc Med* 2018, *28*, (7), 437–441. DOI: 10.1016/j.tcm.2018.02.004.

 doi:10.20944/preprints202605.0616.v1

124. Devries, M.C.; Phillips, S.M. Supplemental Protein in Support of Muscle Mass and Health: Advantage Whey. *J Food Sci* 2015, *80 Suppl 1*, A8–A15. DOI: 10.1111/1750-3841.12802.
125. Mathai, J.K.; Liu, Y.; Stein, H.H. Values for Digestible Indispensable Amino Acid Scores (DIAAS) for Some Dairy and Plant Proteins May Better Describe Protein Quality than Values Calculated Using the Concept for Protein Digestibility-Corrected Amino Acid Scores (PDCAAS). *Br J Nutr* 2017, *117*, (4), 490–499. DOI: 10.1017/S0007114517000125.
126. Hurrell, R.; Egli, I. Iron Bioavailability and Dietary Reference Values. *Am J Clin Nutr* 2010, *91*, (5), 1461S-1467S. DOI: 10.3945/ajcn.2010.28674F.
127. Beulens, J.W.J.; Booth, S.L.; Heuvel, E.G.H.M. van den; et al. The Role of Menaquinones (Vitamin K_2) in Human Health. *Br J Nutr* 2013, *110*, (8), 1357–1368. DOI: 10.1017/S0007114513001013.
128. Hurrell, R.F. Influence of Vegetable Protein Sources on Trace Element and Mineral Bioavailability. *J Nutr* 2003, *133*, (9), 2973S–7S. DOI: 10.1093/jn/133.9.2973S.
129. Pawlak, R.; Lester, S.E.; Babatunde, T. The Prevalence of Cobalamin Deficiency among Vegetarians Assessed by Serum Vitamin B12: A Review of Literature. *Eur J Clin Nutr* 2014, *68*, (5), 541–548. DOI: 10.1038/ejcn.2014.46.
130. Burdge, G.C.; Wootton, S.A. Conversion of Alpha-Linolenic Acid to Palmitic, Palmitoleic, Stearic and Oleic Acids in Men and Women. *Prostaglandins Leukot Essent Fatty Acids* 2003, *69*, (4), 283–290. DOI: 10.1016/s0952-3278(03)00111-x.
131. Rebouche, C.J. Carnitine Function and Requirements during the Life Cycle. *FASEB J* 1992, *6*, (15), 3379–3386.
132. Sandberg, A.-S. Bioavailability of Minerals in Legumes. *Br J Nutr* 2002, *88 Suppl 3*, S281-285. DOI: 10.1079/BJN/2002718.
133. Heaney, R.P.; Weaver, C.M.; Recker, R.R. Calcium Absorbability from Spinach. *Am J Clin Nutr* 1988, *47*, (4), 707–709. DOI: 10.1093/ajcn/47.4.707.
134. Sarwar Gilani, G.; Wu Xiao, C.; Cockell, K.A. Impact of Antinutritional Factors in Food Proteins on the Digestibility of Protein and the Bioavailability of Amino Acids and on Protein Quality. *Br J Nutr* 2012, *108 Suppl 2*, S315-332. DOI: 10.1017/S0007114512002371.
135. Volek, J.S.; Phinney, S.D. A New Look at Carbohydrate-Restricted Diets: Separating Fact From Fiction. *Nutrition Today* 2013, *48*, (2), E1. DOI: 10.1097/NT.0b013e31828814eb; Available online: https://journals.lww.com/nutritiontodayonline/abstract/2013/03000/a_new_look_at_carbohydrate_restricted_diets_.11.aspx.
136. Hallberg, S.J.; McKenzie, A.L.; Williams, P.T.; et al. Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study. *Diabetes Ther* 2018, *9*, (2), 583–612. DOI: 10.1007/s13300-018-0373-9.
137. Volek, J.S.; Feinman, R.D. Carbohydrate Restriction Improves the Features of Metabolic Syndrome. Metabolic Syndrome May Be Defined by the Response

 doi:10.20944/preprints202605.0616.v1

to Carbohydrate Restriction. *Nutr Metab (Lond)* 2005, *2*, 31. DOI: 10.1186/1743-7075-2-31.

138. Bueno, N.B.; Melo, I.S.V. de; Oliveira, S.L. de; et al. Very-Low-Carbohydrate Ketogenic Diet v. Low-Fat Diet for Long-Term Weight Loss: A Meta-Analysis of Randomised Controlled Trials. *Br J Nutr* 2013, *110*, (7), 1178–1187. DOI: 10.1017/S0007114513000548.
139. Shimazu, T.; Hirschey, M.D.; Newman, J.; et al. Suppression of Oxidative Stress by β-Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor. *Science* 2013, *339*, (6116), 211–214. DOI: 10.1126/science.1227166.
140. Neal, E.G.; Chaffe, H.; Schwartz, R.H.; et al. The Ketogenic Diet for the Treatment of Childhood Epilepsy: A Randomised Controlled Trial. *Lancet Neurol* 2008, *7*, (6), 500–506. DOI: 10.1016/S1474-4422(08)70092-9.
141. Freeman, J.M.; Kossoff, E.H.; Hartman, A.L. The Ketogenic Diet: One Decade Later. *Pediatrics* 2007, *119*, (3), 535–543. DOI: 10.1542/peds.2006-2447.
142. Paoli, A. Ketogenic Diet for Obesity: Friend or Foe? *Int J Environ Res Public Health* 2014, *11*, (2), 2092–2107. DOI: 10.3390/ijerph110202092.
143. Masino, S.A.; Ruskin, D.N. Ketogenic Diets and Pain. *J Child Neurol* 2013, *28*, (8), 993–1001. DOI: 10.1177/0883073813487595.
144. Henderson, S.T.; Vogel, J.L.; Barr, L.J.; et al. Study of the Ketogenic Agent AC-1202 in Mild to Moderate Alzheimer's Disease: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. *Nutr Metab (Lond)* 2009, *6*, 31. DOI: 10.1186/1743-7075-6-31.
145. McDonald, T.J.W.; Cervenka, M.C. Ketogenic Diets for Adult Neurological Disorders. *Neurotherapeutics* 2018, *15*, (4), 1018–1031. DOI: 10.1007/s13311-018-0666-8.
146. Klement, R.J. Beneficial Effects of Ketogenic Diets for Cancer Patients: A Realist Review with Focus on Evidence and Confirmation. *Med Oncol* 2017, *34*, (8), 132. DOI: 10.1007/s12032-017-0991-5.
147. Allen, B.G.; Bhatia, S.K.; Anderson, C.M.; et al. Ketogenic Diets as an Adjuvant Cancer Therapy: History and Potential Mechanism. *Redox Biol* 2014, *2*, 963–970. DOI: 10.1016/j.redox.2014.08.002.
148. Naude, C.E.; Schoonees, A.; Senekal, M.; et al. Low Carbohydrate versus Isoenergetic Balanced Diets for Reducing Weight and Cardiovascular Risk: A Systematic Review and Meta-Analysis. *PLoS One* 2014, *9*, (7), e100652. DOI: 10.1371/journal.pone.0100652.
149. Kosinski, C.; Jornayvaz, F.R. Effects of Ketogenic Diets on Cardiovascular Risk Factors: Evidence from Animal and Human Studies. *Nutrients* 2017, *9*, (5), 517. DOI: 10.3390/nu9050517.
150. Porta, M.; Puigdomènech, E.; Ballester, F.; et al. Monitoring Concentrations of Persistent Organic Pollutants in the General Population: The International Experience. *Environ Int* 2008, *34*, (4), 546–561. DOI: 10.1016/j.envint.2007.10.004.
151. Lee, D.-H.; Steffes, M.W.; Sjödin, A.; et al. Low Dose Organochlorine Pesticides and Polychlorinated Biphenyls Predict Obesity, Dyslipidemia, and

 doi:10.20944/preprints202605.0616.v1

Insulin Resistance among People Free of Diabetes. *PLoS One* 2011, *6*, (1), e15977. DOI: 10.1371/journal.pone.0015977.

152. Lennerz, B.S.; Mey, J.T.; Henn, O.H.; et al. Behavioral Characteristics and Self-Reported Health Status among 2029 Adults Consuming a "Carnivore Diet." *Curr Dev Nutr* 2021, *5*, (12), nzab133. DOI: 10.1093/cdn/nzab133.
153. Cordain, L.; Toohey, L.; Smith, M.J.; et al. Modulation of Immune Function by Dietary Lectins in Rheumatoid Arthritis. *Br J Nutr* 2000, *83*, (3), 207–217. DOI: 10.1017/s0007114500000271.
154. Fasano, A. Intestinal Permeability and Its Regulation by Zonulin: Diagnostic and Therapeutic Implications. *Clin Gastroenterol Hepatol* 2012, *10*, (10), 1096–1100. DOI: 10.1016/j.cgh.2012.08.012.
155. Vojdani, A. Lectins, Agglutinins, and Their Roles in Autoimmune Reactivities. *Altern Ther Health Med* 2015, *21 Suppl 1*, 46–51.
156. Chassaing, B.; Koren, O.; Goodrich, J.K.; et al. Dietary Emulsifiers Impact the Mouse Gut Microbiota Promoting Colitis and Metabolic Syndrome. *Nature* 2015, *519*, (7541), 92–96. DOI: 10.1038/nature14232.
157. Fardet, A.; Rock, E. Perspective: Reductionist Nutrition Research Has Meaning Only within the Framework of Holistic and Ethical Thinking. *Adv Nutr* 2018, *9*, (6), 655–670. DOI: 10.1093/advances/nmy044.
158. Singh, R.K.; Chang, H.-W.; Yan, D.; et al. Influence of Diet on the Gut Microbiome and Implications for Human Health. *J Transl Med* 2017, *15*, (1), 73. DOI: 10.1186/s12967-017-1175-y.
159. David, L.A.; Maurice, C.F.; Carmody, R.N.; et al. Diet Rapidly and Reproducibly Alters the Human Gut Microbiome. *Nature* 2014, *505*, (7484), 559–563. DOI: 10.1038/nature12820.
160. Lee, D.-H.; Steffes, M.W.; Sjödin, A.; et al. Low Dose of Some Persistent Organic Pollutants Predicts Type 2 Diabetes: A Nested Case-Control Study. *Environ Health Perspect* 2010, *118*, (9), 1235–1242. DOI: 10.1289/ehp.0901480.
161. Cordain, L. Cereal Grains: Humanity´s Double-Edged Sword.; Available online: https://karger.com/books/book/2319/chapter/5725621/Cereal-Grains-Humanity-s-Double-Edged-Sword.
162. Mattson, M.P. Hormesis Defined. *Ageing Res Rev* 2008, *7*, (1), 1–7. DOI: 10.1016/j.arr.2007.08.007.
163. Calabrese, E.J. Hormesis: Why It Is Important to Toxicology and Toxicologists. *Environ Toxicol Chem* 2008, *27*, (7), 1451–1474. DOI: 10.1897/07-541.
164. Zhang, Y.; Gordon, G.B. A Strategy for Cancer Prevention: Stimulation of the Nrf2-ARE Signaling Pathway. *Mol Cancer Ther* 2004, *3*, (7), 885–893.
165. Del Rio, D.; Rodriguez-Mateos, A.; Spencer, J.P.E.; et al. Dietary (Poly)Phenolics in Human Health: Structures, Bioavailability, and Evidence of Protective Effects against Chronic Diseases. *Antioxid Redox Signal* 2013, *18*, (14), 1818–1892. DOI: 10.1089/ars.2012.4581.

 doi:10.20944/preprints202605.0616.v1

166. Holmes, R.P.; Kennedy, M. Estimation of the Oxalate Content of Foods and Daily Oxalate Intake. *Kidney Int* 2000, *57*, (4), 1662–1667. DOI: 10.1046/j.1523-1755.2000.00010.x.
167. Messina, M. Impact of Soy Foods on the Development of Breast Cancer and the Prognosis of Breast Cancer Patients. *Forsch Komplementmed* 2016, *23*, (2), 75–80. DOI: 10.1159/000444735.
168. Chen, L.-R.; Ko, N.-Y.; Chen, K.-H. Isoflavone Supplements for Menopausal Women: A Systematic Review. *Nutrients* 2019, *11*, (11), 2649. DOI: 10.3390/nu11112649.
169. Catassi, C.; Bai, J.C.; Bonaz, B.; et al. Non-Celiac Gluten Sensitivity: The New Frontier of Gluten Related Disorders. *Nutrients* 2013, *5*, (10), 3839–3853. DOI: 10.3390/nu5103839.
170. Fasano, A. Zonulin, Regulation of Tight Junctions, and Autoimmune Diseases. *Ann N Y Acad Sci* 2012, *1258*, (1), 25–33. DOI: 10.1111/j.1749-6632.2012.06538.x.
171. Sapone, A.; Bai, J.C.; Ciacci, C.; et al. Spectrum of Gluten-Related Disorders: Consensus on New Nomenclature and Classification. *BMC Med* 2012, *10*, 13. DOI: 10.1186/1741-7015-10-13.
172. Holmes, R.P.; Kennedy, M. Estimation of the Oxalate Content of Foods and Daily Oxalate Intake. *Kidney Int* 2000, *57*, (4), 1662–1667. DOI: 10.1046/j.1523-1755.2000.00010.x.
173. Noonan, S.C.; Savage, G.P. Oxalate Content of Foods and Its Effect on Humans. *Asia Pac J Clin Nutr* 1999, *8*, (1), 64–74.
174. Khan, S.R. Crystal-Induced Inflammation of the Kidneys: Results from Human Studies, Animal Models, and Tissue-Culture Studies. *Clin Exp Nephrol* 2004, *8*, (2), 75–88. DOI: 10.1007/s10157-004-0292-0.
175. Khan, S.R. Hyperoxaluria-Induced Oxidative Stress and Antioxidants for Renal Protection. *Urol Res* 2005, *33*, (5), 349–357. DOI: 10.1007/s00240-005-0492-4.
176. Siener, R.; Seidler, A.; Hönow, R. Oxalate-Rich Foods. *Food Sci. Technol* 2020, *41*, 169–173. DOI: https://doi.org/10.1590/fst.10620; Available online: https://www.scielo.br/j/cta/a/TfJ6dZ8CD88rGwfqdKpqyVf/?lang=en.
177. Curhan, G.C.; Willett, W.C.; Speizer, F.E.; et al. Twenty-Four-Hour Urine Chemistries and the Risk of Kidney Stones among Women and Men. *Kidney Int* 2001, *59*, (6), 2290–2298. DOI: 10.1046/j.1523-1755.2001.00746.x.
178. Curhan, G.C.; Rimm, E.B.; Willett, W.C.; et al. Regional Variation in Nephrolithiasis Incidence and Prevalence among United States Men. *J Urol* 1994, *151*, (4), 838–841. DOI: 10.1016/s0022-5347(17)35101-7.
179. Mulay, S.R.; Kulkarni, O.P.; Rupanagudi, K.V.; et al. Calcium Oxalate Crystals Induce Renal Inflammation by NLRP3-Mediated IL-1β Secretion. *J Clin Invest* 2013, *123*, (1), 236–246. DOI: 10.1172/JCI63679.
180. Thamilselvan, S.; Khan, S.R.; Menon, M. Oxalate and Calcium Oxalate Mediated Free Radical Toxicity in Renal Epithelial Cells: Effect of Antioxidants. *Urol Res* 2003, *31*, (1), 3–9. DOI: 10.1007/s00240-002-0286-x.

 doi:10.20944/preprints202605.0616.v1

181. Hatch, M.; Freel, R.W. A Human Strain of Oxalobacter (HC-1) Promotes Enteric Oxalate Secretion in the Small Intestine of Mice and Reduces Urinary Oxalate Excretion. *Urolithiasis* 2013, *41*, (5), 379–384. DOI: 10.1007/s00240-013-0601-8.
182. Knight, J.; Jiang, J.; Assimos, D.G.; et al. Hydroxyproline Ingestion and Urinary Oxalate and Glycolate Excretion. *Kidney Int* 2006, *70*, (11), 1929–1934. DOI: 10.1038/sj.ki.5001906.
183. Knight, J.; Deora, R.; Assimos, D.G.; et al. The Genetic Composition of Oxalobacter Formigenes and Its Relationship to Colonization and Calcium Oxalate Stone Disease. *Urolithiasis* 2013, *41*, (3), 187–196. DOI: 10.1007/s00240-013-0566-7.
184. Savage, G.P.; Vanhanen, L.; Mason, S.M.; et al. Effect of Cooking on the Soluble and Insoluble Oxalate Content of Some New Zealand Foods. *Journal of Food Composition and Analysis* 2000, *13*, (3), 201–206. DOI: 10.1006/jfca.2000.0879; Available online: https://www.sciencedirect.com/science/article/pii/S0889157500908792.
185. Lee, Y.-M.; Jacobs, D.R.; Lee, D.-H. Persistent Organic Pollutants and Type 2 Diabetes: A Critical Review of Review Articles. *Front Endocrinol (Lausanne)* 2018, *9*, 712. DOI: 10.3389/fendo.2018.00712.
186. Domingo, J.L.; Bocio, A. Levels of PCDD/PCDFs and PCBs in Edible Marine Species and Human Intake: A Literature Review. *Environ Int* 2007, *33*, (3), 397–405. DOI: 10.1016/j.envint.2006.12.004.
187. Abdul, K.S.M.; Jayasinghe, S.S.; Chandana, E.P.S.; et al. Arsenic and Human Health Effects: A Review. *Environ Toxicol Pharmacol* 2015, *40*, (3), 828–846. DOI: 10.1016/j.etap.2015.09.016.
188. Muncke, J. Exposure to Endocrine Disrupting Compounds via the Food Chain: Is Packaging a Relevant Source? *Sci Total Environ* 2009, *407*, (16), 4549–4559. DOI: 10.1016/j.scitotenv.2009.05.006.
189. Evans, J.L.; Goldfine, I.D.; Maddux, B.A.; et al. Oxidative Stress and Stress-Activated Signaling Pathways: A Unifying Hypothesis of Type 2 Diabetes. *Endocr Rev* 2002, *23*, (5), 599–622. DOI: 10.1210/er.2001-0039.
190. Rani, V.; Deep, G.; Singh, R.K.; et al. Oxidative Stress and Metabolic Disorders: Pathogenesis and Therapeutic Strategies. *Life Sci* 2016, *148*, 183–193. DOI: 10.1016/j.lfs.2016.02.002.
191. Nicolopoulou-Stamati, P.; Maipas, S.; Kotampasi, C.; et al. Chemical Pesticides and Human Health: The Urgent Need for a New Concept in Agriculture. *Front Public Health* 2016, *4*, 148. DOI: 10.3389/fpubh.2016.00148.
192. Mesnage, R.; Antoniou, M.N. Facts and Fallacies in the Debate on Glyphosate Toxicity. *Front Public Health* 2017, *5*, 316. DOI: 10.3389/fpubh.2017.00316.
193. Myers, J.P.; Antoniou, M.N.; Blumberg, B.; et al. Concerns over Use of Glyphosate-Based Herbicides and Risks Associated with Exposures: A Consensus Statement. *Environ Health* 2016, *15*, 19. DOI: 10.1186/s12940-016-0117-0.

 doi:10.20944/preprints202605.0616.v1

194. Samsel, A.; Seneff, S. Glyphosate, Pathways to Modern Diseases II: Celiac Sprue and Gluten Intolerance. *Interdiscip Toxicol* 2013, *6*, (4), 159–184. DOI: 10.2478/intox-2013-0026; Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3945755/.
195. Landrigan, P.J.; Goldman, L.R. Children's Vulnerability to Toxic Chemicals: A Challenge and Opportunity to Strengthen Health and Environmental Policy. *Health Aff (Millwood)* 2011, *30*, (5), 842–850. DOI: 10.1377/hlthaff.2011.0151.
196. Van Bruggen, A.H.C.; He, M.M.; Shin, K.; et al. Environmental and Health Effects of the Herbicide Glyphosate. *Sci Total Environ* 2018, *616–617*, 255–268. DOI: 10.1016/j.scitotenv.2017.10.309.
197. Carpenter, D.O. Health Effects of Persistent Organic Pollutants: The Challenge for the Pacific Basin and for the World. *Rev Environ Health* 2011, *26*, (1), 61–69. DOI: 10.1515/reveh.2011.009.
198. La Merrill, M.; Birnbaum, L.S. Childhood Obesity and Environmental Chemicals. *Mt Sinai J Med* 2011, *78*, (1), 22–48. DOI: 10.1002/msj.20229.
199. Jones, D.P. Radical-Free Biology of Oxidative Stress. *Am J Physiol Cell Physiol* 2008, *295*, (4), C849-868. DOI: 10.1152/ajpcell.00283.2008.
200. Fang, Y.-Z.; Yang, S.; Wu, G. Free Radicals, Antioxidants, and Nutrition. *Nutrition* 2002, *18*, (10), 872–879. DOI: 10.1016/s0899-9007(02)00916-4.
201. Lykkesfeldt, J.; Poulsen, H.E. Is Vitamin C Supplementation Beneficial? Lessons Learned from Randomised Controlled Trials. *Br J Nutr* 2010, *103*, (9), 1251–1259. DOI: 10.1017/S0007114509993229.
202. Monteiro, C.A.; Moubarac, J.-C.; Cannon, G.; et al. Ultra-Processed Products Are Becoming Dominant in the Global Food System. *Obes Rev* 2013, *14 Suppl 2*, 21–28. DOI: 10.1111/obr.12107.
203. Barrea, L.; Muscogiuri, G.; Frias-Toral, E.; et al. Nutrition and Immune System: From the Mediterranean Diet to Dietary Supplementary through the Microbiota. *Crit Rev Food Sci Nutr* 2021, *61*, (18), 3066–3090. DOI: 10.1080/10408398.2020.1792826.