

Beyond dietary restriction: Towards next-generation precision diets for healthy aging

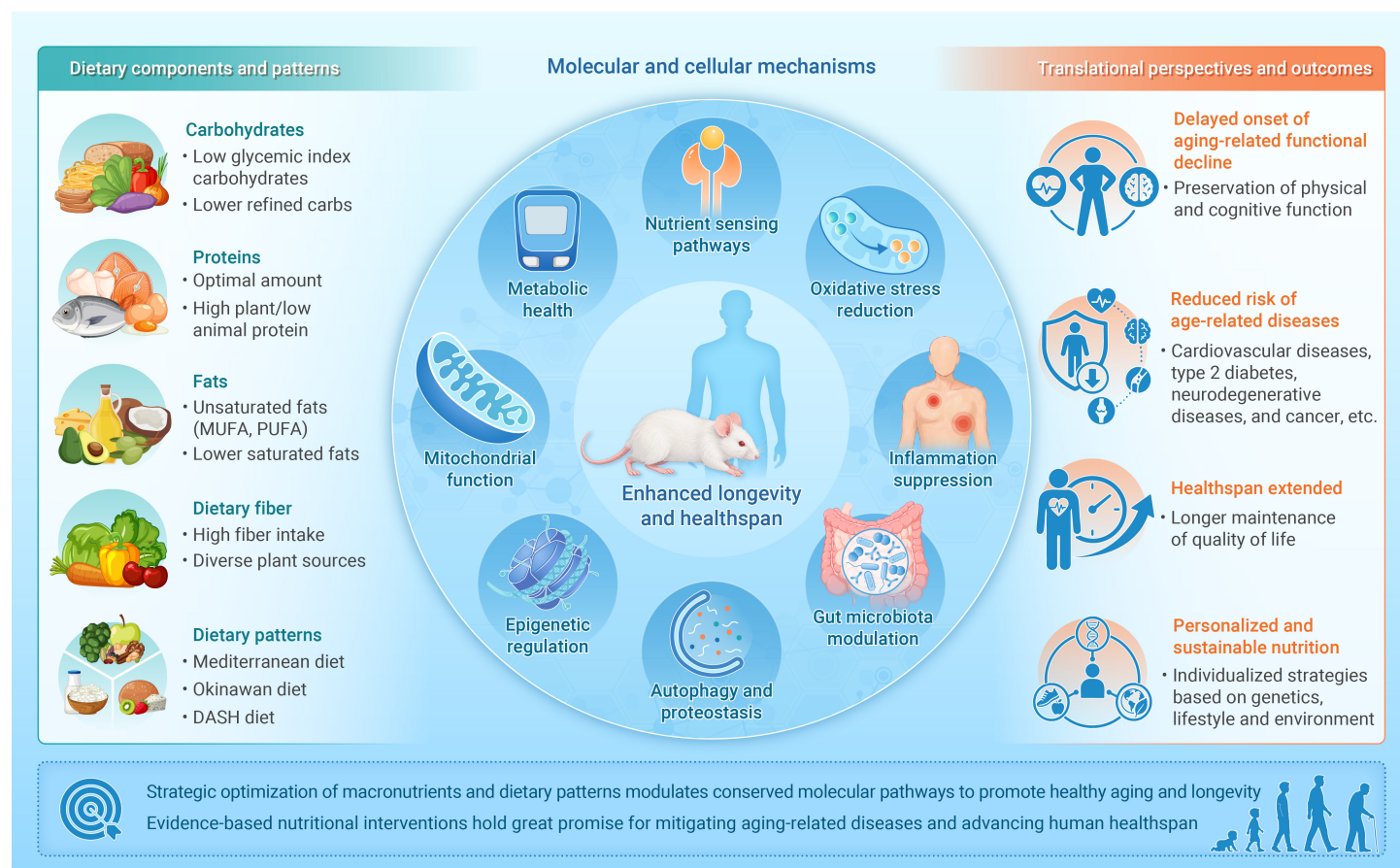
Jintao Huang,¹ Dejian Huang,^{2,3} and Ziyun Wu^{1,*}

*Correspondence: wuziyun@sjtu.edu.cn

Received: June 4, 2026; Accepted: August 19, 2026; Published Online: August 29, 2026; <https://doi.org/10.59717/j.xinn-nutri.2026.100034>

© 2026 The Author(s). This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>).

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Diet shapes aging through both the amount of food eaten and the balance and quality of nutrients.
- Evidence from animals and human populations shows that nutrition can influence lifespan and healthspan.
- Younger adults need enough protein, while older adults may benefit from more plant foods and fiber.
- Future diets may be personalized using genes, gut microbes, glucose patterns, and digital monitoring data.

Beyond dietary restriction: Towards next-generation precision diets for healthy aging

Jintao Huang,¹ Dejian Huang,^{2,3} and Ziyun Wu^{1,*}

¹Department of Food Science and Engineering, School of Agriculture and Biology, Shanghai Jiao Tong University, Shanghai 200240, China

²National University of Singapore (Suzhou) Research Institute, Suzhou 215123, China

³Department of Food Science and Technology, National University of Singapore, Singapore 117542, Singapore

*Correspondence: wuziyun@sjtu.edu.cn

Received: June 4, 2026; Accepted: August 19, 2026; Published Online: August 29, 2026; <https://doi.org/10.59717/j.xinn-nutri.2026.100034>

© 2026 The Author(s). This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>).

Citation: Huang J., Huang D. and Wu Z. (2026). Beyond dietary restriction: Towards next-generation precision diets for healthy aging. *The Innovation Nutrition* 1:100034.

Longevity is governed by complex interactions between genes and environment, in which diet is among the most powerful modifiable determinants. Although classical dietary restriction reliably extends lifespan, evidence from more than thirty large prospective cohorts and meta-analyses summarized in this review indicates that meaningful longevity benefits can be achieved without caloric restriction by optimizing macronutrient composition. This precision-nutrition strategy targets carbohydrate quality, protein sources and specific amino acids, lipid class, and dietary fiber, and adapts these choices to age, sex, genetic background, metabolic phenotype, and gut microbiome composition. This review integrates findings from model organisms, mechanistic investigations, and large-scale prospective cohorts to describe how macronutrients and their combinations modulate lifespan-associated nutrient-sensing pathways. An age-stratified macronutrient framework and a longevity dietary pyramid are proposed, both of which address how nutritional recommendations should evolve from young adulthood through old age. The framework is further situated within a broader precision-nutrition paradigm that incorporates continuous glucose monitoring, multi-omics profiling, microbiome-guided personalization, time-restricted eating, and emerging digital tools such as wearable monitoring and artificial-intelligence-assisted diet design. Together, these elements bridge mechanistic insight and population-level evidence, and provide a foundation for precision diets aimed at extending healthspan and promoting healthy longevity.

INTRODUCTION

The global population is undergoing profound demographic aging. The number of individuals aged 80 years and above is projected to more than triple between 2017 and 2050, reaching 425 million.¹ This unprecedented demographic shift reflects sustained advances in nutrition, living standards, sanitation, and healthcare.² However, advanced age carries markedly elevated risk of chronic and aging-related diseases, including cardiovascular disease (CVD), type 2 diabetes, autoimmune disorders, cataracts, osteoporosis, neurodegenerative diseases, and multiple cancers. In a large primary-care population of 1,751,841 Scottish residents, over 90% of individuals above 65 years were affected by at least one chronic condition and more than 70% by multimorbidity;³ comparable patterns of high multimorbidity prevalence have since been confirmed in cohorts from the United States, China, and across Europe.⁴ Therapeutic strategies that target the fundamental biology of aging, rather than addressing each aging-associated disease in isolation, hold transformative potential for global health.²

Longevity is shaped by interactions between genetic predisposition and environmental factors, among which diet is one of the most powerful and modifiable modulators. Dietary restriction (DR), defined as a reduction in food intake without malnutrition,⁵ has been recognized since the 1930s as a reproducible intervention for lifespan extension across organisms ranging from yeast to mammals.^{6–7} Practical limitations of severe DR cannot be overlooked: such regimens are difficult to adopt and maintain, and may induce reproductive impairment, menstrual irregularities, osteoporotic fractures, and cardiac arrhythmias.⁸ Dietary restriction mimetics that recapitulate the benefits of DR without prolonged fasting or caloric deficit have therefore emerged as a major priority for healthy aging in humans. Specific macronutrient composition (the relative proportions of carbohydrates, proteins, amino acids, and fatty acids) can exert profound effects on health and longevity even in the

absence of overall caloric restriction (CR).⁹ These effects are documented in invertebrate models such as yeast (*Saccharomyces cerevisiae*),¹⁰ nematodes (*Caenorhabditis elegans*),¹¹ and fruit flies (*Drosophila melanogaster*),¹² and in mammalian systems including rats (*Rattus norvegicus*)⁶ and mice (*Mus musculus*).⁵ Substantial longevity benefits in humans may therefore be achievable without reducing total food intake, through optimization of macronutrient balance.

Identifying optimal macronutrient ratios for human diets nonetheless remains a substantial challenge.¹³ Insights from model organisms illuminate the conserved nutrient-sensing pathways that link dietary input to aging (Figure 1). The four primary pathways are those regulated by sirtuins (SIRT1), the mechanistic target of rapamycin (mTOR), adenosine 5'-monophosphate-activated protein kinase (AMPK), and the insulin/insulin-like growth factor-1 (IGF-1)/growth hormone (GH) axis.^{7,14–15} Reduced mTOR and insulin/IGF-1/GH signaling, together with elevated AMPK and SIRT1 activity, drive enhanced mitochondrial biogenesis, autophagy, optimized metabolism, resistance to oxidative stress, genomic integrity, and regulated protein synthesis.¹⁴ Beyond these molecular insights, large prospective human cohorts now provide complementary evidence that macronutrient composition modulates all-cause mortality at the population level, independent of total energy intake. In the PURE study spanning 18 countries (n = 135,335),¹⁶ the ARIC cohort and its meta-analysis of seven international cohorts (pooled n > 430,000),¹⁷ and the Nurses' Health Study with 32-year follow-up,¹⁸ both very low and very high carbohydrate intake were linked to increased mortality, while plant-derived substitutions were protective. This review therefore focuses on the four macronutrients (carbohydrates, proteins, fats, and dietary fiber) that constitute the principal source of energy and building blocks of the organism and most directly modulate nutrient-sensing pathways linked to aging. Findings from model organisms, mechanistic studies, dietary patterns, and large-scale epidemiological cohorts across geographic regions are integrated, and a practical longevity dietary pyramid together with age-specific macronutrient recommendations is proposed to facilitate translation into dietary practice.

Carbohydrates

Carbohydrate quantity, quality, and source exert profound effects on aging. Consumption of high-glycemic-index (GI) foods elevates postprandial glucose and insulin and may enhance insulin/IGF-1 signaling.¹⁹ The insulin/IGF-1 signaling (IIS) pathway initiates intracellular cascades involving Akt and mTOR that regulate cellular growth, proliferation, and metabolic homeostasis. In parallel, the AMPK pathway is robustly activated under glucose restriction or energy scarcity;²⁰ once activated, AMPK promotes glycolysis and fatty acid β -oxidation while suppressing de novo lipogenesis and gluconeogenesis. Both pathways are evolutionarily conserved from yeast to human.^{21–22}

Large prospective cohorts and meta-analyses published since 2010 have consistently demonstrated a non-linear (U- or J-shaped) association between carbohydrate intake and all-cause mortality (Table 1).^{16–18,23–32} Moderate carbohydrate consumption (approximately 50–55% of energy) is associated with the lowest mortality risk, whereas both very low-carbohydrate (< 40% energy) and very high-carbohydrate (> 70% energy) intakes are linked to elevated risk. These associations are strongly modulated by carbohydrate quality, source (plant- versus animal-derived replacement macronutrients), glycemic index or load, fiber content, and participant characteristics

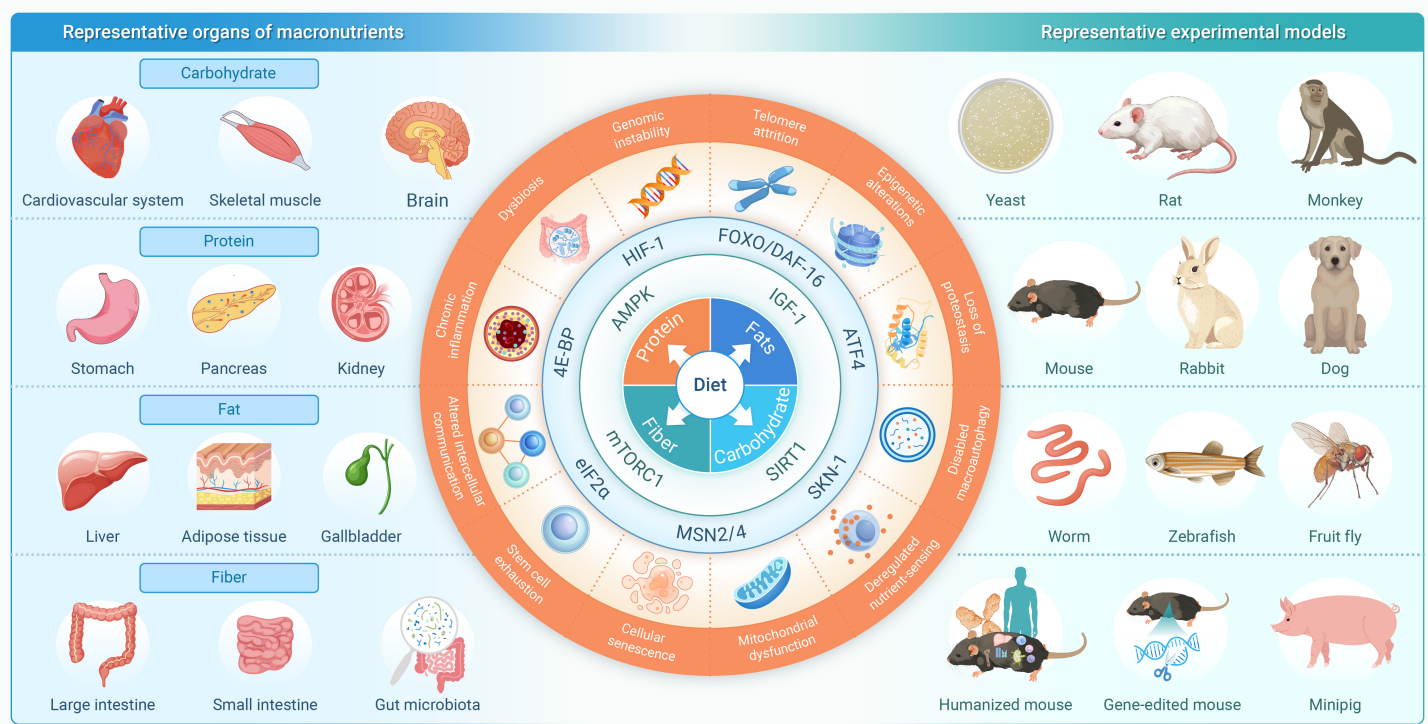


Figure 1. Nutritional signaling pathways involved in macronutrient regulation of aging The four macronutrients (carbohydrates, proteins, fats, and dietary fiber) modulate aging and longevity by acting on four conserved nutrient-sensing pathways (IIS, mTOR, AMPK, SIRT1) and downstream effectors. These pathways act through transcription factors and other downstream effectors that influence the twelve hallmarks of aging (around the figure: 1. genomic instability; 2. telomere attrition; 3. epigenetic alterations; 4. loss of proteostasis; 5. disabled macroautophagy; 6. deregulated nutrient-sensing; 7. mitochondrial dysfunction; 8. cellular senescence; 9. stem cell exhaustion; 10. altered intercellular communication; 11. chronic inflammation; 12. dysbiosis) and the physiological functions of target organs across the cardiovascular, musculoskeletal, neural, hepatic, adipose, gastrointestinal, and microbial systems. Abbreviations: IIS, insulin/IGF-1 signaling; mTOR, mechanistic target of rapamycin; AMPK, AMP-activated protein kinase; SIRT1, sirtuins; SKN-1, *C. elegans* Nrf2 ortholog; 4E-BP, eIF4E-binding protein; HIF-1, hypoxia-inducible factor 1; FOXO/DAF-16, FOXO family / *C. elegans* ortholog; ATF4, activating transcription factor 4; eIF2α, eukaryotic initiation factor 2α; MSN2/4, *S. cerevisiae* stress-response transcription factors.

Table 1. Key prospective cohorts and meta-analyses on carbohydrate intake and all-cause mortality.

Ref	Population (n / follow-up)	Exposure	Main finding
23	NHS + HPFS; 129,716; 20-26 y	LCD score; animal vs plant	Animal LCD ↑ mortality; vegetable-based ↓ mortality
16	PURE, 18 countries; 135,335; 7.4 y	Carbohydrate % energy	High carb (>60%) ↑ all-cause mortality; fat intake ↓ mortality
17	ARIC + meta of 7 cohorts; pooled 432,179; 16-25 y	Carbohydrate % energy	U-shaped; risk lowest at moderate intake; plant substitution protective
24	NHANES + meta of 9 cohorts; pooled 462,934; 6-16 y	LCD score quartiles	LCD ↑ mortality, stronger in non-obese
25	UK Biobank; 195,658; 10.6 y	Carbohydrate % energy (non-linear)	Non-linear; higher carb (50-70%) ↑ mortality
26	KNHANES; 42,192; up to 8 y	Carbohydrate % energy (U-shaped)	Lowest risk at 50-60% energy from carbohydrate
27	NHANES; 37,233; 8 y	LCD score (healthy vs unhealthy)	Healthy plant-based LCD protective; unhealthy detrimental
28	JPHC; ~90,000; 15 y	LCD score quintiles	Both LCD and HCD ↑ mortality; plant-based LCD protective
29	Meta of 10 cohorts; 421,022; 6-26 y	LCD score (plant vs animal)	Plant-based LCD ↓ mortality; animal LCD null/risk
30	J-MICC; 81,333; 8.9 y	Carbohydrate % energy	Low carb ↑ mortality in men; high carb ↑ in women
31	KoGES; large Korean; 10.1 y	Carbohydrate % energy by diabetes	Higher carb ↑ mortality in diabetes
18	NHS midlife; 47,513; ~32 y	Carbohydrate quantity and quality	U-shaped; high-quality carbs ↓ mortality, ↑ healthy aging
32	Korean cohort, high-carb background; 9.2 y	Carbohydrate % energy	Very low carb (<55%) ↑ all-cause and CVD mortality

Notes: NHS = Nurses' Health Study; HPFS = Health Professionals Follow-up Study; PURE = Prospective Urban Rural Epidemiology; ARIC = Atherosclerosis Risk in Communities; NHANES = National Health and Nutrition Examination Survey; KNHANES = Korea NHANES; JPHC = Japan Public Health Center; J-MICC = Japan Multi-Institutional Collaborative Cohort; KoGES = Korean Genome and Epidemiology Study; LCD = low-carbohydrate diet. All estimates multivariable-adjusted.

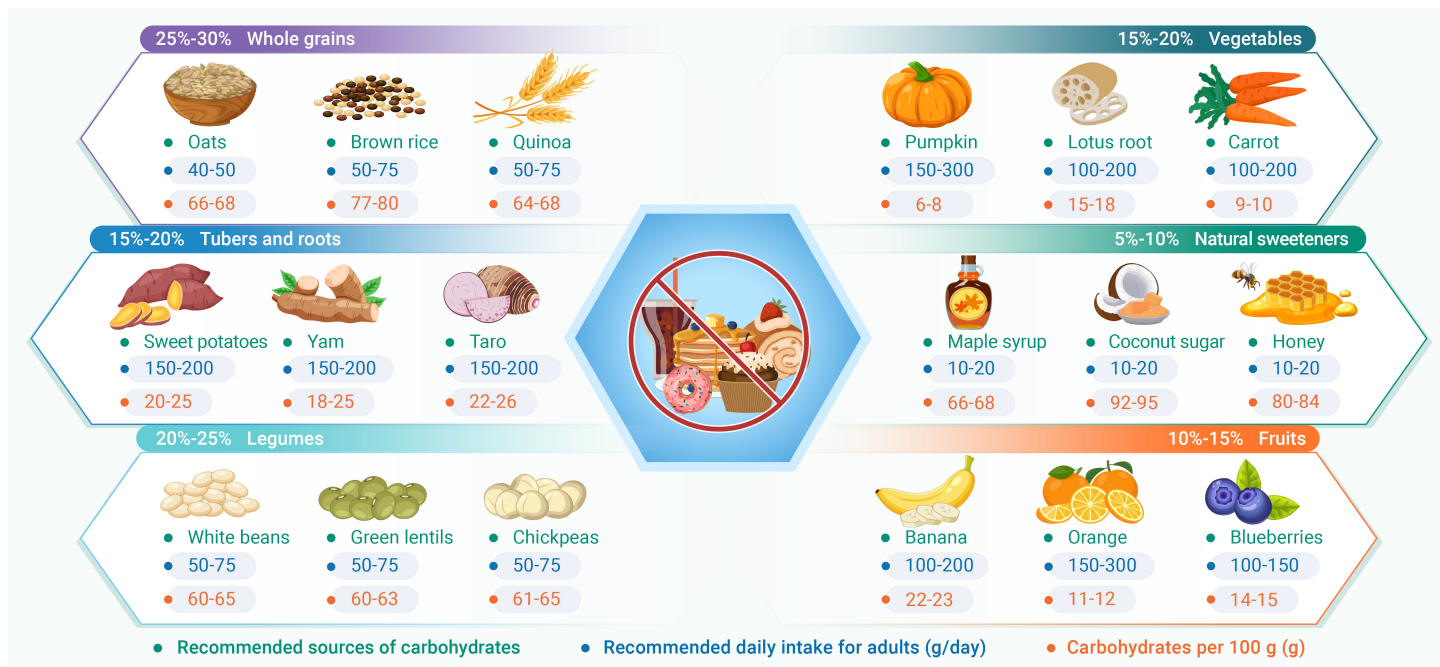


Figure 2. Recommended carbohydrate sources for a longevity diet Six longevity-oriented carbohydrate groups with proportional contribution to total carbohydrate intake: whole grains (25-30%; e.g., oats, brown rice, quinoa), legumes (20-25%; white beans, chickpeas), vegetables (15-20%; pumpkin, carrots), tubers and roots (15-20%; sweet potato, yam, taro), fruits (10-15%; banana, citrus, berries), and natural sweeteners (5-10%; small amounts of maple syrup, honey). Refined carbohydrates and added-sugar beverages are not recommended. Percentages are based on the recommended daily carbohydrate intake (45-65% of total energy).

such as age, obesity status, and diabetes prevalence. Animal-based low-carbohydrate diets consistently confer higher risk, whereas plant-based or high-quality carbohydrate patterns are protective. The evidence derives from multivariable Cox proportional hazards models in large cohorts with follow-up durations ranging from 6 to more than 20 years.

The effects of carbohydrate intake on lifespan and healthspan vary with age, genetic background, and underlying health status. Carbohydrate restriction extends lifespan in healthy wild-type mice without pre-existing conditions;³³ in mice with congenital or acquired diseases, increased carbohydrate availability may instead reduce mortality.³⁴ Sugar type also exerts effects on aging.³⁵ Selection of low-GI foods helps maintain stable blood glucose and improves insulin sensitivity, contributing to delayed aging and extended healthspan.³⁶⁻³⁸ Although direct evidence linking low-GI diets to increased human lifespan remains limited, preclinical studies show lifespan extension with low-GI interventions in aged mice,³⁷ and epidemiological data indicate that lower dietary GI and glycemic load are associated with greater odds of healthy aging and reduced incidence of aging-related diseases.

Recommended carbohydrate sources and proportions for a longevity diet are summarized in Figure 2. Suggested intake ranges align with the Acceptable Macronutrient Distribution Range (AMDR) of 45-65% of total energy for carbohydrates set jointly by the Institute of Medicine, the European Food Safety Authority (EFSA), and the World Health Organization (WHO), with cereal and tuber intake of 200-400 g/day (raw weight) supported by the Dietary Guidelines for Chinese Residents (2022), the Dietary Guidelines for Americans (2020-2025), and the Australian NHMRC. The proportional contributions represent idealized distributions in high-quality, low-GI dietary patterns; actual intake should be individualized according to age, sex, body weight, physical activity, genetic background, and underlying health conditions.

Proteins and amino acids

Protein intake influences health and longevity beyond its classical metabolic roles. The protein leverage hypothesis posits that a strong appetite for protein drives overconsumption of fats and carbohydrates when animals are offered a protein-diluted diet.³⁹ While this phenomenon has been documented in mice, *Drosophila*, and primates, human evidence remains limited and indirect: controlled feeding studies in healthy adults show modest protein-driven compensation in energy intake (~10-15%), and observational analyses

of NHANES and UK Biobank participants are consistent with but do not confirm the magnitude observed in animals.³⁹⁻⁴⁰ Whether protein leverage operates with comparable strength in free-living humans therefore requires direct verification. Debate persists regarding whether the life-extending effects of DR arise primarily from CR or from protein restriction (PR).⁴¹ Emerging evidence indicates that PR or selective limitation of methionine and tryptophan can account for many beneficial effects previously attributed to CR and to growth hormone/IGF-1 receptor deficiency (GHRD) mutations, mediated at least in part by reduced circulating IGF-1.⁴² In contrast, a high-protein, low-carbohydrate diet shortens lifespan in both male and female mice.⁹

Associations between dietary protein and all-cause mortality in humans are highly context-dependent (Table 2).⁴²⁻⁵² In middle-aged adults, higher total or animal-derived protein intake is frequently associated with modestly elevated mortality, mediated by IGF-1/mTOR activation. Plant protein intake consistently shows inverse associations with mortality. In older adults (typically ≥ 65-70 years), moderate-to-higher protein intake appears protective, counteracting sarcopenia and frailty. Substitution analyses highlight the advantage of replacing animal protein, particularly processed red meat, with plant protein. Data on individual amino acids remain limited but generally indicate neutral-to-inverse associations.

Methionine restriction (MR), implemented by reducing dietary methionine to approximately 20% of control levels (0.86% to 0.17% by weight) while maintaining isocaloric intake, robustly extends lifespan in rodents.⁵³ MR increases median and maximum lifespan in rats and mice by up to 30-45%, attenuates immune senescence and lens aging, lowers circulating IGF-1, insulin, and glucose, and enhances stress resistance.⁵⁴ These benefits persist when MR is initiated in middle or late life, improving neuromuscular function, frailty index, and metabolic health without caloric reduction.⁵⁵ Comparable lifespan extension occurs in progeroid mouse models, where MR ameliorates chronic inflammation and DNA damage responses.⁵⁶ Translation of these rodent effects to humans requires caution: short-term human trials of sulfur amino acid restriction (typically 2-16 weeks) have shown metabolic improvements without adverse effects on epigenetic clocks, but long-term safety, feasibility, and effects on lean mass in older adults remain unresolved.

Tryptophan, an essential aromatic amino acid and serotonin precursor, also modulates longevity. In male Swiss albino mice, a diet restricted in tryptophan (~50% reduction) extended median lifespan from 616 to 683 days

Table 2. Key prospective cohorts and meta-analyses on protein/amino acid intake and all-cause mortality.

Ref	Population (n / follow-up)	Exposure	Main finding
42	NHANES III; 6,381; ~18 y	Total protein % energy by age	High protein ↑ mortality in midlife; protective in older adults
43	NHS + HPFS; 131,342; 20-26 y	Animal vs plant protein	Animal protein weakly ↑ mortality; plant ↓ mortality
44	JPHC; 70,696; ~18 y	Plant vs animal protein	Plant protein ↓ all-cause and CVD mortality
45	Meta of 32 cohorts; 715,128; 3.5-32 y	Total/animal/plant protein	Total and plant protein ↓ mortality; plant ↓ CVD mortality
46	Rotterdam + meta; ~400,000+; 10-20 y	Total/animal/plant protein	Total protein ↑ mortality via animal sources
47	NIH-AARP; 416,104; 16 y	Plant vs animal protein	Plant protein ↓ all-cause and CVD mortality
48	NHANES-linked; nationwide; ~10+ y	Dietary BCAA	Higher BCAA ↓ all-cause mortality
49	CHAMP, Australia; men ≥70 y; ~3.7 y	Total/animal/plant	Moderate total optimal; plant ↓ mortality
50	KAWP, Japan; adults ≥85 y; 3.3 y	Total protein % energy	Higher protein ↓ mortality in very old; fish protein contributes
51	Network meta-analysis; multiple cohorts	Animal vs plant substitution	Plant for animal substitution ↓ all-cause mortality
52	NHANES III updated; ~15,937; 12-18 y	Usual animal vs plant protein	Neither protein source adversely associated with mortality

Notes: CHAMP = Concord Health and Ageing in Men Project; KAWP = Kawasaki Aging and Wellbeing Project; BCAA = branched-chain amino acids. All estimates multivariable-adjusted.

(~11% increase), with reductions in body weight and organ mass.⁵⁷

Glycine has emerged as a potent modulator of longevity. Diets supplemented with 8% or 12% glycine extend lifespan in rats, increasing median lifespan from 88 to 113 weeks while improving blood glucose, insulin, IGF-1, and triglycerides.⁵⁸ The primary mechanism involves enhanced glycine N-methyltransferase activity, which clears excess methionine and toxic metabolites.⁵⁸ In genetically heterogeneous mice, 8% glycine supplementation produced statistically significant median lifespan extension (4% in males, 6% in females) and maximum lifespan gains of 2% and 7%, respectively.⁵⁹ Glycine also reduces non-esterified fatty acids, adipocyte hypertrophy, visceral fat, and blood pressure in sucrose-fed rats⁶⁰ and modulates innate and adaptive immune responses, attenuating chronic inflammation in type 2 diabetes models.⁶¹ Population-level validation in humans remains required.

Branched-chain amino acids (BCAAs: leucine, isoleucine, valine) regulate metabolic health with context-dependent longevity effects. A BCAA-enriched mixture in middle-aged (9-month-old) mice increased median lifespan by 12.3% (774 to 869 days), mediated by SIRT1-dependent mitochondrial biogenesis in cardiac and skeletal muscle and improving endurance and motor coordination.⁶² Chronic high-BCAA intake from weaning, in contrast, promotes hyperphagia and obesity and shortens lifespan by 5-10%.⁶³ A 67% reduction in dietary isoleucine initiated in young adult mice (6 months) extended median lifespan by 7% to 33% in a sex-dependent manner while reducing adiposity.⁶³ Excessive BCAA consumption early in life therefore carries metabolic risk, whereas strategic restriction or targeted supplementation in later life shows promise for healthy aging.

Excessive animal protein intake can accelerate aging, whereas plant-based proteins generally do not increase the risk of aging-related diseases or shorten lifespan, due to lower sulfur amino acid and methionine content that otherwise activates mTOR and stimulates GH release.⁶⁴

Recommended protein sources and proportional contributions for a longevity diet are summarized in Figure 3. These recommendations align with the FAO/WHO/UNU expert consultation on protein and amino acid requirements and with longevity dietary guidance, emphasizing high-quality protein from legumes, dairy, eggs, poultry, fish, and seafood that accounts for over 50% of total protein intake. Combined daily intake of fish, poultry, lean meat, and eggs is suggested at approximately 120-200 g.

Fats

As a major energy source, lipids profoundly influence health and longevity, providing the highest energy density per unit mass among macronutrients. Alterations in lipid metabolism, particularly lipid signaling, constitute an important mechanism underlying healthy aging,⁶⁵ associated with adiposity reduction and modulation of IGF-1 signaling.⁶⁶ Excess adiposity is itself a primary driver of cardiovascular morbidity in aging populations: longitudinal

data from over 10 million adults indicate that each 5 kg/m² increase in midlife BMI above 25 is associated with 30-40% higher all-cause mortality and substantially elevated cardiovascular mortality, with abdominal adiposity contributing independent risk through ectopic lipid deposition, low-grade inflammation, and impaired insulin signaling.⁶⁷⁻⁶⁸ Dietary fat composition therefore matters not only through direct effects on nutrient-sensing pathways but also indirectly through modulation of adiposity and downstream cardiometabolic health.

Recent epidemiological evidence demonstrates that associations between dietary fat intake and all-cause mortality are strongly modulated by fat type, source (plant versus animal), and isocaloric replacement nutrient (Table 3).⁶⁹⁻⁷⁷ Higher intakes of saturated fatty acids (SFA) and trans-fatty acids (TFA) are linked to modestly elevated mortality risk, whereas polyunsaturated fatty acids (PUFA) and plant-derived monounsaturated fatty acids (MUFA) show inverse associations. Total fat intake often exhibits neutral-to-inverse relations when fat quality is high. Substitution analyses underscore the benefit of replacing SFA or TFA with PUFA or plant-derived MUFA.

Dietary fat type and quality are critical determinants of longevity. Modifications in fat content or fatty acid composition extend lifespan by modulating systemic metabolism, particularly evident in reproductively impaired animal models.⁷⁸ Supplementation with additional butter shortened lifespan in male rats, whereas equivalent or higher fat supplementation with sunflower oil did not produce a comparable shortening in mice.⁷⁹ Polyunsaturated fatty acids (PUFAs) are widely regarded as beneficial: walnuts and deep-sea fish, rich in ω-3 PUFAs including α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), are associated with reduced all-cause mortality.⁸⁰

Lipid-specific interventions extend lifespan and healthspan in animals, indicating that lipid metabolism directly regulates aging rather than merely correlating with aging-related disease. Supplementation of *Daphnia* with ω-6 PUFAs (linoleic acid and related fatty acids) enhances starvation resistance and extends lifespan under ad libitum feeding.⁸¹ In *C. elegans* and human epithelial cells, ω-6 PUFA supplementation activates autophagy, improving survival under nutrient deprivation and delaying aging.⁸² In mice, ω-3 PUFAs prolong reproductive lifespan, whereas high ω-6 PUFA diets diminish reproductive success.⁸³

Additional lipid interventions support the regulatory role of lipid metabolism in aging. The fatty acid 10-hydroxy-2-decenoic acid, a major component of royal jelly, extends lifespan in *C. elegans*.⁸⁴ Overexpression of the fatty acid desaturase *FAT-4* prolongs nematode lifespan and augments oxidative stress resistance, while lysosomal lipase *LIPL-4* expression hydrolyzes lipids such as cholesterol esters and triglycerides to extend lifespan.⁸⁵ Intestinal overexpression of *FAT-7* in *C. elegans* increases lifespan despite higher fat stores.⁸⁶ In long-lived nematode mutants, fatty acid chain length and suscep-

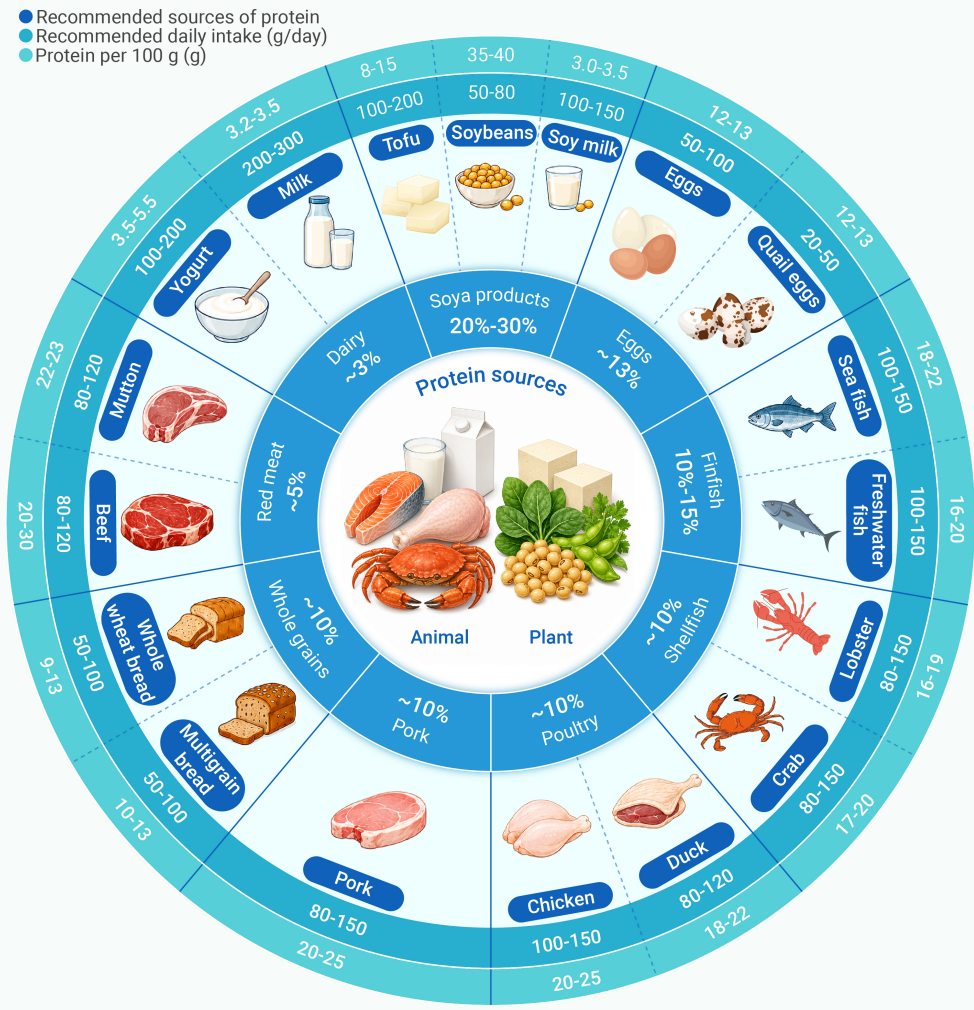


Figure 3. Recommended protein sources for a longevity diet Protein sources are divided into nine categories with recommended contributions to total daily protein intake: soya products (20-30%), eggs (~13%), finfish (10-15%), shellfish (~10%), poultry (chicken/duck, ~10%), red meat (beef/mutton, ~5%), lean pork (~10%), whole grains (~10%), dairy products (~3%). High-quality protein from legumes, dairy, eggs, poultry, fish, and seafood should account for over 50% of total protein intake.

estradiol improves metabolic parameters, decreases adiposity and inflammation, and extends median lifespan in a sex-specific manner, predominantly in males.⁸⁹ Diverse interventions targeting lipid metabolism therefore promote longevity across species, typically by enhancing metabolic efficiency and attenuating oxidative and inflammatory stress.

Longevity-promoting genetic mouse models typically increase fat reserves, indicating that adequate or strategically elevated fat storage exerts beneficial effects under specific conditions.⁹⁰⁻⁹¹ Wild-type mice are generally less efficient at mobilizing fat stores and show more pronounced lifespan extension with dietary restriction.⁹² Surgical removal of visceral fat in rats improves insulin sensitivity and extends lifespan,⁹³ underscoring the detrimental role of ectopic or visceral fat in normal aging.

When C57BL/6 mice were fed a high-fat diet throughout life, males experienced a reduction in average lifespan by approximately 144 days, whereas females showed no significant change.⁹⁴ This sexual dimorphism likely reflects estrogen-dependent regulation of lipid metabolism and thermogenesis. Consistent with this, dietary supplementation with 17 α -

ability to oxidation are reduced, suggesting an optimized lipid profile enriched in shorter, less oxidizable fatty acids promotes longevity by attenuating oxidative damage.⁸⁷

In mammals, genetic deficiency of diacylglycerol O-acyltransferase 1 (DGAT1) inhibits triglyceride synthesis, reduces fat storage, enhances fatty acid oxidation, and improves systemic lipid metabolism, producing leanness and extended lifespan independent of caloric restriction.⁸⁸ The steroid 17 α -

estradiol (4.8 ppm) had no effect on female lifespan but increased median lifespan in males by about 12%.⁸⁹

Future research should elucidate the molecular mechanisms underlying differential effects of dietary fats on aging, with emphasis on AMPK and SIRT1 signaling that may mediate the beneficial actions of PUFAs.⁹⁵ Dietary fat quality outweighs quantity for public health, supporting consumption of healthy fats from nuts, olive oil, and fatty fish while discouraging saturated

Table 3. Key prospective cohorts and meta-analyses on dietary fat intake and all-cause mortality.

Ref	Population (n / follow-up)	Exposure	Main finding
69	NHS + HPFS; 126,233; up to 32 y	Specific fats (extreme quintiles)	SFA, TFA $\uparrow$ mortality; PUFA, MUFA $\downarrow$ mortality; 5% SFA $\rightarrow$ PUFA: HR 0.73
70	NIH-AARP; large US; ~15 y	Specific fats (extreme quintiles)	SFA, TFA, animal MUFA $\uparrow$ mortality; plant MUFA, PUFA, marine ω -3 $\downarrow$ mortality
71	NHANES + meta of 29 cohorts; 1,164,029; 6-16 y	Total/MUFA/PUFA/SFA	Total fat, MUFA, PUFA $\downarrow$ mortality; SFA $\uparrow$ mortality
72	Meta of 19 cohorts; 1,013,273	5% energy increments by type	High SFA $\uparrow$ mortality; high PUFA $\downarrow$ mortality
73	NIH-AARP (updated); >400,000; ~16 y	Plant vs animal MUFA/PUFA	Plant-derived fats $\downarrow$ mortality; animal-derived fats null/adverse
74	NHANES; ~44,920; 11.8 y	SFA by chain length	Short-chain SFA (butyrate) $\downarrow$ mortality; long-chain neutral
75	NHS + HPFS; 65,179 adults; 26-year follow-up	Change in fatty acid intake	Total fat, PUFA, MUFA $\uparrow \rightarrow \downarrow$ mortality; TFA $\uparrow \rightarrow \uparrow$ mortality
76	Pooled international (>5 million)	Total fat and subtypes	PUFA $\downarrow$ all-cause mortality; SFA and trans fat $\uparrow$ risk
77	NHANES; 49,884; 10 y	SFA and PUFA quintiles	Higher SFA $\uparrow$, higher PUFA $\downarrow$ mortality; substitution lowers risk

Notes: SFA = saturated fatty acids; TFA = trans-fatty acids; PUFA = polyunsaturated fatty acids; MUFA = monounsaturated fatty acids.

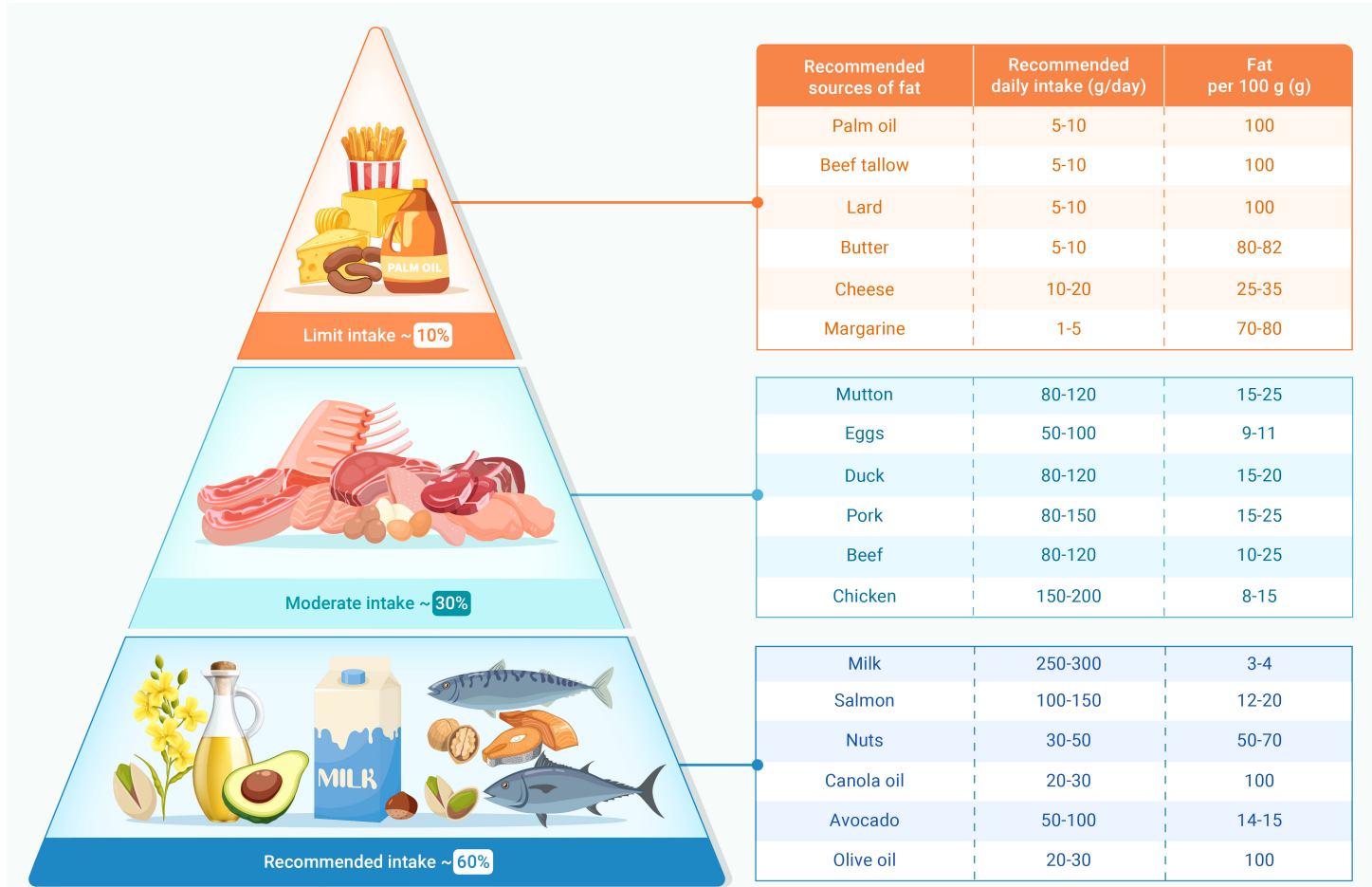


Figure 4. Recommended fat sources for a longevity diet Three-tier pyramid showing recommended distribution by quality. Bottom tier (recommended, ~60%): vegetable oils (canola, peanut, olive oil), nuts, fatty fish, milk, and avocado, providing unsaturated fatty acids. Middle tier (moderate intake, ~30%): lean meats including beef, mutton, chicken, and duck. Top tier (limit intake, ~10%): saturated fats from margarine, cheese, butter, lard, beef tallow, and palm oil. Percentages refer to total daily fat intake ($\leq 30\%$ of energy).

and trans fats. Further studies on optimal dietary patterns and fat sources tailored to genetic predispositions and sex-specific responses will be essential for personalized nutritional guidelines (Figure 4). Current recommendations suggest that fat should contribute no more than 30% of total daily energy.⁹⁶ Given the roles of fat metabolism in energy storage, signaling, and membrane homeostasis, emphasis on high-quality fats is advisable rather than their elimination. Emerging data also raise concerns about very-long-term ketogenic-like diets, including potential increases in cellular senescence and liver abnormalities in animal models.

Dietary fiber

Dietary fiber is broadly classified into soluble and insoluble types with distinct physicochemical properties. Soluble fibers (inulin, pectin, β -glucans) dissolve in water to form viscous gels and are readily fermented by gut microbiota, yielding short-chain fatty acids (SCFAs) including acetate, propionate, and butyrate. Insoluble fibers (cellulose, lignin) increase fecal bulk, accelerate intestinal transit, and are less fermentable. In invertebrates and rodents, these properties modulate gut microbiota composition, metabolic signaling, and stress resistance relevant to lifespan regulation.⁹⁷ Representative fiber-rich food sources and recommended intake distribution are summarized in Figure 5.

Epidemiological studies have consistently demonstrated a robust, inverse, dose-dependent association between dietary fiber and all-cause mortality (Table 4).⁹⁸⁻¹⁰⁷ Higher total fiber consumption (highest versus lowest quintile or tertile, or per 10 g/day increment) is associated with 10-23% lower mortality risk, with stronger protective effects for insoluble fiber, cereal/whole-grain fiber, and vegetable fiber than for soluble or fruit fiber alone.

In *Drosophila melanogaster*, dietary fiber supplementation extends lifes-

pan in a sex- and fiber-type-dependent manner.¹⁰⁸ Lifelong addition of a commercial mixed-fiber syrup (0.25% or 1% w/v) prolonged mean half-life in both sexes, with absolute lifespan increased by approximately 11% in females. Inulin at 5% or 10% extended mean lifespan in males by 53.83% and 61.62%, with median lifespan increases of 172.63% and 182.19%, respectively; females showed no benefit or slight reduction.¹⁰⁹ These effects were associated with enhanced gut microbiota diversity, upregulation of stress- and longevity-related genes, and improved intestinal homeostasis, independent of caloric restriction.

In mice, a high-fiber diet (15-35% total fiber, replacing 30% w/w of macronutrients with indigestible cellulose) provided ad libitum recapitulated the transcriptomic and metabolomic signatures of caloric restriction (down-regulation of inflammatory and translational pathways, upregulation of autophagy and lipid metabolism) and improved motor function, cognition, and metabolic homeostasis across young, middle-aged, and aged animals.¹¹⁰ A diet diluted with 50% cellulose extended lifespan in aging C57BL/6J mice with a 27% reduction in protein synthesis rate but unchanged liver protein half-life.¹¹¹ In models of accelerated aging, butyrate or its prodrug tributyrin, a primary metabolite of microbial fiber fermentation, extends healthspan and lifespan (median ~25%, maximum >70% in some models) by restoring histone acylation, strengthening intestinal barrier function, and mitigating multimorbidity.¹¹²

Macronutrient-balanced diet for healthy longevity

The ratio of dietary macronutrients influences metabolic health, chronic disease risk, and longevity. Researchers proposed that the key determinant of diet-mediated longevity effects is not total caloric intake but rather the balance between protein and non-protein energy sources.¹¹³ Australian stud-



Figure 5. Recommended fiber sources for a longevity diet Six fiber-rich food groups with proportional contribution to total daily fiber intake (25-30 g/day): whole grains (~30%; oats, brown rice, whole-wheat bread), legumes (~20%; black beans, soybeans, chickpeas), vegetables (~20%; broccoli, carrots, spinach), fruits (~15%; apples with skin, pears with skin, blueberries), nuts and seeds (~10%; almonds, walnuts, chia seeds), and tubers (~5%; sweet potato, potato with skin, Chinese yam). Recommended daily intake ranges and fiber content per 100 g are indicated.

Table 4. Key prospective cohorts and meta-analyses on dietary fiber intake and all-cause mortality.

Ref	Population (n / follow-up)	Exposure	Main finding
98	NIH-AARP; 388,122; 9 y	Fiber intake quintiles	Inverse with total, CVD, infectious, respiratory mortality
99	Meta of 7 cohorts; 908,135	Total fiber (highest vs lowest)	Higher fiber ↓ mortality; cereal and vegetable fiber strongest
100	Meta of 17 cohorts; 982,411	Total fiber and per 10 g/d	Significantly ↓ all-cause mortality; dose-response
101	Meta of 42 cohorts; 1,752,848; 12.4 y	Total fiber and per 10 g/d	Substantial ↓ all-cause mortality; dose-response
102	JPHC; 91,946; 16.8 y	Total/soluble/insoluble fiber	Fiber from fruits, beans, vegetables ↓ mortality
103	Korean cohort; large; 10.1 y	Total fiber quintiles	Higher fiber ↓ all-cause and CVD mortality
104	Meta of 28 cohorts; 1,613,885	Total and subtypes	All subtypes except fruit fiber ↓ mortality; dose-response
105	Updated meta of 64 cohorts; 3,512,828	Total fiber and subtypes/sources	Highest vs lowest: 23% ↓ all-cause mortality
106	Meta of 185 cohorts + 58 RCTs; ~135M PY	Total fiber and whole grains	15-30% ↓ mortality, CVD, CHD, stroke, T2D, CRC; optimum 25-29 g/d
107	NHANES MetS subgroup; ~10 y	Total fiber tertiles	Higher fiber ↓ mortality in MetS; threshold near recommended level

Notes: All estimates multivariable-adjusted. Source-specific benefits consistently strongest for insoluble, cereal, and vegetable fiber.

ies have further linked dietary macronutrient composition to age-specific mortality.¹¹⁴ In early life, mortality is minimized when fat and carbohydrate each contribute approximately 40-45% of energy, with 16% from protein. In later life, the lowest mortality risk is observed at approximately 65% carbohydrate, 24% fat, and 11% protein. Balanced fat and carbohydrate intake therefore optimizes survival early in life, whereas a shift toward higher carbohydrate and lower fat favors longevity in older age.

A fundamental principle of life history theory is the trade-off between reproduction and longevity. High-protein, low-carbohydrate (HPLC) diets optimize reproductive parameters including uterine mass, follicle counts, testicular mass, and epididymal sperm counts.¹¹⁵ In contrast, mice maintained on a low-protein, high-carbohydrate (LPHC) diet exhibit the longest lifespan.¹¹⁶ Similar divergence is observed in other species: macronutrient

compositions that maximize longevity differ markedly from those that maximize reproductive success in *Teleogryllus commodus* and *Drosophila*.¹¹⁷

Nutritional geometry has provided a powerful framework on nutrition and aging by integrating calories, macronutrient ratios, and interactive effects while accounting for compensatory feeding behavior under ad libitum conditions.¹¹⁸ State-space modeling examines how animals regulate intake and balance nutrient availability. A limitation persists: although the framework captures quantitative macronutrient interactions, qualitative aspects of the three major macronutrients (distinct types of fats, carbohydrates, and proteins) have yet to be fully integrated.¹¹⁹

Individual nutrients exert distinct effects on longevity, implying that optimal dietary structure in free-living humans requires balanced consumption of multiple foods. Numerous studies have examined overall dietary patterns and

Table 5. Key prospective cohorts and meta-analyses on longevity dietary patterns and all-cause mortality.

Ref	Population (n / follow-up)	Exposure	Main finding
124	Meta of 29 cohorts; 1,676,901; 7-25 y	Mediterranean diet score	Higher MD adherence ↓ all-cause mortality; linear dose-response
125	Meta; >500,000	DASH adherence	Higher DASH ↓ all-cause and cause-specific mortality
126	Systematic review; 152 cohorts + 1 RCT	Multiple nutrient-dense patterns	Plant-rich, fish-inclusive patterns ↓ mortality regardless of label
127	JPHC (Okinawan elements); ~90,000+; 15-18 y	Japanese diet index JDI8	Higher adherence ↓ all-cause and CVD mortality
128	Women's Health Study; 25,315; 24.7 y	MD score (high vs low)	23% ↓ all-cause mortality; biomarkers mediate ~45%
129	Meta of 14 cohorts	PDI (plant-based diet index)	Higher PDI ↓ all-cause and cancer mortality
130	40 RCTs; 35,548; ≥9 months	Seven structured dietary programs	MD and low-fat programs ↓ mortality
131	Meta of cohorts; >1 million	hPDI (healthful plant-based)	Higher hPDI ↓ mortality; unhealthy plant-based ↑ risk
132	JPHC; 92,969; 18.9 y	Japanese Diet Index variants	Higher adherence ↓ all-cause and CVD mortality in both sexes

Notes: MD = Mediterranean diet; DASH = Dietary Approaches to Stop Hypertension; PDI = plant-based diet index; hPDI = healthful plant-based diet index; RCT = randomized controlled trial.

longevity.¹²⁰ A prominent example is the traditional Okinawan diet in Japan. In 2005, Okinawan women showed a life expectancy of 86.88 years, 1.13 years above the national Japanese average of 85.75 years. Okinawan men also recorded notably higher life expectancy in 1985 (78.64 versus 74.95 years), though this advantage has since diminished. The diet is predominantly plant-based, featuring whole grains, vegetables, fruits, modest amounts of fish, and small portions of lean meat.¹²¹ Compared with the typical Japanese diet, it contains approximately 20% fewer calories, representing a natural form of caloric restriction combined with nutrient-dense foods widely regarded as a modulator of longevity.¹²² Okinawan elders who maintain this pattern consume a low protein-to-carbohydrate ratio (~1:10 or lower), with protein accounting for ≤ 10% of total caloric intake.¹²³ This ratio closely mirrors the macronutrient balance shown to maximize lifespan in model organisms.¹¹⁶

Recent epidemiological studies demonstrate that adherence to plant-rich longevity dietary patterns (Mediterranean, DASH, healthful plant-based, Okinawan-style) is associated with approximately 10-25% lower all-cause mortality (Table 5).¹²⁴⁻¹³² These benefits hold across multivariable-adjusted Cox proportional hazards models accounting for age, sex, energy intake, smoking, physical activity, BMI, and comorbidities, with follow-up durations of 7 to 26 years. Substitution analyses and food quality (plant versus animal sources) emerge as critical modifiers.

The Mediterranean diet (MD) is widely recognized as an exemplary healthy eating pattern. The MD reflects the traditional dietary habits of populations in Greece, Spain, France, southern Italy, and other southern European nations.¹³³ Greater adherence to the MD can extend human life expectancy by several years¹³⁴ and is associated with reduced risk of dementia, depression, and several cancers including breast, respiratory, and bladder cancers.¹³⁵⁻¹³⁶ A growing literature suggests that the benefits of the MD are mediated in part through epigenetic mechanisms: adherence to the MD has been associated with favorable DNA methylation profiles at loci regulating inflammation and lipid metabolism, slower epigenetic clock progression, and reduced expression of senescence-associated secretory phenotype (SASP) markers in peripheral blood.¹³⁷⁻¹³⁸ These observations help explain the durable benefits of the MD beyond its nutrient composition alone.

The ketogenic diet (KD), originally developed by Wilder in the 1920s for refractory epilepsy, is conceptually distinct from popular low-carbohydrate approaches. The classic therapeutic KD restricts carbohydrate intake to ≤ 5% of total calories (25-50 g/day), with approximately 75% from fat and 20% from protein, with the explicit goal of inducing sustained nutritional ketosis (β-hydroxybutyrate ≥ 0.5 mmol/L). Popular low-carb or modified Atkins diets, by contrast, permit 50-130 g carbohydrate/day and rarely achieve true ketosis. This distinction is crucial when interpreting health outcomes: most cohort

evidence on low-carbohydrate diets reflects the latter, while animal lifespan data come from the former. Evidence indicates that the KD can be effective for obesity management,¹³⁹ but robust support for benefits in cancer, Alzheimer's, or Parkinson's disease remains limited. In older adults with hyperglycaemia or diabetes, the KD may serve as a useful therapeutic strategy. In C57BL/6 mice, long-term KD feeding significantly extended median lifespan and overall survival, with preservation of physiological function, increased histone acetylation, and tissue-specific modulation of mTORC1 signaling.³³ Three caveats temper enthusiasm for translating these findings to human longevity practice. First, prospective cohort evidence (Table 1) consistently shows that very-low-carbohydrate diets, particularly those emphasizing animal sources, are associated with neutral or modestly elevated all-cause mortality. Second, emerging data raise concerns about cellular senescence: chronic KD feeding in mice increases markers of senescence in cardiac and hepatic tissues, an effect not observed with intermittent or cyclical KD regimens.¹⁴⁰ Third, long-term adherence in free-living adults is poor, and abrupt discontinuation may produce metabolic rebound. The KD therefore appears most appropriate as a time-limited therapeutic tool under medical supervision rather than as a sustained longevity strategy.

Cross-species translation of macronutrient effects on lifespan

The magnitude of macronutrient effects on lifespan varies substantially across species, complicating direct extrapolation from model organisms to humans. Methionine restriction extends median lifespan by 30-45% in rats and mice⁵³⁻⁵⁴ but, in short-term human trials, reduces IGF-1 by 7-14% and improves insulin sensitivity without measurable change in epigenetic age. Isoleucine restriction extends mouse lifespan by 7-33% sex-dependently,⁶³ corresponding human data are restricted to observational analyses linking higher BCAA intake to insulin resistance in some cohorts but neutral or inverse mortality associations in others (Table 2). Inulin supplementation extends *Drosophila* lifespan by over 50% in males;¹⁰⁹ human randomized trials show modest improvements in glycemic control, lipid profile, and microbiome diversity but no longevity endpoints. KD extends mouse lifespan³³, while human cohort data show neutral or adverse mortality associations for sustained low-carbohydrate intake (Table 1). Three patterns emerge across these comparisons. First, effects on biomarkers (IGF-1, insulin sensitivity, inflammation, microbiome diversity) translate reasonably well between rodents and humans, supporting the use of these intermediates as surrogate endpoints in human trials. Second, effects on lifespan extension are systematically attenuated in mammals with longer baseline lifespan, consistent with diminishing returns from interventions in slower-aging species. Third, sex- and genotype-specific responses in mice (for

example, 17 α -estradiol benefits restricted to males; isoleucine restriction effects varying by genetic background) are likely amplified in genetically and environmentally heterogeneous human populations, arguing for stratified rather than uniform dietary recommendations.

PRECISION NUTRITION

What makes a longevity diet precise: A balanced diet underpins health, yet attention to total energy or any single nutrient remains insufficient. Existing dietary guidelines, including the Dietary Guidelines for Chinese Residents (2022), the Dietary Guidelines for Americans, EFSA Dietary Reference Values, and Australian NHMRC, primarily target chronic disease prevention and basic nutritional balance across broad life stages. These frameworks were not designed with healthy aging and longevity as the central objective, particularly regarding dynamic macronutrient ratios that may better support late-life healthspan. Precision nutrition extends these population-level recommendations to the individual level by integrating multiple layers of biological and behavioral information: chronological age and biological age, sex, genotype (including IGF-1 pathway variants, APOE, and FTO), metabolic phenotype (fasting glucose, postprandial glycemic response, lipid subfractions, inflammatory markers), gut microbiome composition, and habitual dietary pattern.^{141,142} A practical precision-nutrition framework comprises four operational components: (i) baseline phenotyping through clinical biomarkers, multi-omics, and continuous physiological monitoring; (ii) goal definition (lifespan extension, healthspan, sarcopenia prevention, cardiometabolic risk reduction); (iii) personalized intervention selection from a defined set of macronutrient compositions, timing strategies, and food matrices; and (iv) iterative monitoring with feedback adjustment.¹⁴²

Continuous glucose monitoring and postprandial glycemic personalization: Continuous glucose monitoring (CGM) has shifted dietary recommendations from population averages to individualized glycemic responses. The PREDICT 1 study demonstrated that postprandial glycemic, insulinemic, and triglyceride responses to identical meals vary up to ten-fold across individuals, with the variation predicted by gut microbiome composition, sleep, physical activity, and meal context rather than by the food alone.¹⁴¹ Machine-learning algorithms trained on CGM and microbiome data can predict individual responses and guide personalized recommendations that improve glycemic control beyond standard advice.¹⁴³ For longevity, the relevance lies in cumulative glycemic exposure across decades, which contributes to advanced glycation end-product accumulation, vascular aging, and cognitive decline.

Gut microbiome as a mediator of macronutrient effects: The gut microbiome mediates substantial portions of the longevity effects attributed to dietary fiber, plant proteins, and polyphenols. Fiber fermentation produces short-chain fatty acids that signal through G-protein-coupled receptors (GPR41, GPR43, GPR109A) to modulate intestinal barrier integrity, systemic inflammation, and host metabolism.¹⁴⁴ The composition of the microbiome in centenarians is enriched in producers of butyrate and secondary bile acid metabolites, with reduced abundance of pro-inflammatory taxa.¹⁴⁵ Microbiome-guided nutrition uses 16S rRNA or shotgun metagenomic sequencing of stool to predict food responses and tailor fiber and prebiotic recommendations. Smaller controlled studies show that microbiome-personalized diets outperform standardized Mediterranean recommendations on postprandial glucose and inflammatory markers over 12 months.¹⁴³⁻¹⁴⁴

Meal timing and time-restricted eating: Circadian biology has emerged as a fourth dimension of precision nutrition alongside quantity, quality, and composition. Time-restricted eating (TRE), in which food intake is confined to a daily window of 6-10 hours, aligns nutrient delivery with circadian metabolic rhythms.¹⁴⁶ Preclinical studies show that TRE extends lifespan in *Drosophila* and improves metabolic health in mice independent of caloric reduction. Human single-arm pilot trial of 8-10-hour TRE windows demonstrate modest weight loss, improved insulin sensitivity, and reduced blood pressure, although effects on cardiometabolic biomarkers beyond those attributable to caloric reduction remain debated.¹⁴⁷ Early evidence suggests that early-day TRE windows (eating window concluded before 16:00-18:00) produce greater metabolic benefit than late-day windows of equal duration, consistent with circadian regulation of insulin sensitivity and thermogenesis.¹⁴⁶ Long-term effects on healthspan and lifespan in humans require dedicated trials.

Ultra-processed foods: The increasing dominance of ultra-processed

foods (UPF) in modern diets represents a major and largely overlooked driver of accelerated aging. UPF, defined by the NOVA classification as industrial formulations made primarily from substances derived from foods plus additives,¹⁴⁸ now contribute over 50% of energy intake in many high-income countries and rising shares in middle-income countries. Prospective cohorts consistently link higher UPF consumption to all-cause mortality (15-30% higher risk in the highest versus lowest quintile of intake), cardiovascular disease, type 2 diabetes, depression, and cognitive decline, with associations persisting after adjustment for nutrient composition.¹⁴⁹⁻¹⁵⁰ Plausible mechanisms include the disruption of food matrix properties that govern glycemic and lipemic response, exposure to emulsifiers and artificial sweeteners that alter the microbiome, and exposure to chemicals migrating from packaging. A practical precision-nutrition recommendation that crosses all life stages is therefore to limit UPF intake, with macronutrient quality emphasized over isolated nutrient adequacy.

Sex as a biological variable: Sex modifies the longevity response to nearly every macronutrient examined. In dietary fat studies, lifelong high-fat feeding shortens male but not female mouse lifespan,⁹⁴ and 17 α -estradiol extends male but not female lifespan.⁸⁹ In amino acid studies, isoleucine restriction produces larger lifespan extension in males,⁶³ and glycine supplementation produces larger relative gains in females.⁵⁹ In fiber studies, inulin extends male but not female *Drosophila* lifespan.¹⁰⁹ Mechanisms include estrogen-dependent regulation of lipid metabolism and thermogenesis, sex-specific gut microbiome composition, and divergent expression of nutrient-sensing pathway components. The implication for human precision nutrition is that uniform macronutrient targets across sexes are unlikely to be optimal, and sex-stratified recommendations should become standard in longevity dietary guidance.

Age-stratified dietary recommendations: The optimal macronutrient composition shifts across the life course. A recommended longevity dietary model adjusted by age is presented in Table 6, with an explicit indication of the strength of supporting evidence for each recommendation. In early adulthood, macronutrient distributions that support growth, sexual maturation, and reproductive success are appropriate, with protein at 15-20% of energy. The midlife transition window, broadly defined as 40-50 years on the basis of cohort evidence showing accelerated rises in cardiometabolic risk, sarcopenia onset, and epigenetic age in this decade,^{18,38} constitutes a critical period during which optimal nutrition shifts toward suppression of growth-promoting pathways such as IIS and mTOR, favoring lower animal protein (10-15%), a higher plant-protein share, and higher dietary fiber (40-60 g/day). In older adulthood (65+ years), sarcopenia and frailty dominate, and protein intake should be raised again (15-20% of energy, preferentially from fish and plant sources) while abundant fiber continues to support microbiome-derived SCFA production and metabolic health. The longevity dietary pyramid summarized in Figure 6 is distinct from previously proposed pyramids (e.g., the Mediterranean diet pyramid and the USDA Food Pyramid/MyPlate) in three respects: (i) it includes a Base Layer explicitly representing fluid intake, sufficient sleep, consistent work schedules and regular exercise as foundational determinants of longevity rather than depicting food groups in isolation; (ii) it integrates the four macronutrients along a continuous quality gradient rather than ranking food groups by recommended frequency; and (iii) it is intended to be read in conjunction with the age-stratified recommendations in Table 6, making it a dynamic rather than a static guidance tool.

FUTURE DIRECTIONS

Translating preclinical promise into effective human longevity interventions requires concrete progress along four lines.

Specific endpoints for next-generation longevity trials: Future randomized controlled trials should move beyond mortality and body composition to incorporate biological age clocks (epigenetic age acceleration measured by GrimAge, PhenoAge, and DunedinPACE), pace-of-aging metrics, and validated frailty indices as primary or co-primary endpoints. Multi-omics endpoints should include plasma proteomic aging signatures, metabolomic markers of nutrient-sensing pathway activation (branched-chain amino acid catabolism, ketone bodies, methylation cycle intermediates), and longitudinal stool metagenomics. A minimum trial duration of three to five years is required to capture meaningful change in biological age clocks; shorter trials

Table 6. Recommended macronutrient intake for a longevity-oriented dietary model, with evidence strength.

Age	Carbohydrate	Protein	Fat	Fiber (g/d)	Evidence
Infants (0-2 y)	40-50% (mainly lactose)	7-15% (mostly milk)	40-50% (ω -rich)	2-10	Moderate
Children (2-18 y)	45-55% (>40% whole grains)	15-25% (varied)	30-40% (mostly healthy)	10-20	Moderate
Adults (19-35 y)	50-55% (>60% whole grains)	10-20% (less red meat)	15-25% (mostly healthy)	20-40	High
Midlife (36-64 y)	50-55% (mostly whole grains)	10-15% (more plant-based)	10-20% (mostly healthy)	40-60	High
Older (≥ 65 y)	50-60% (mostly whole grains)	15-20% (mostly plant-based)	10-15% (mostly healthy)	20-40	Moderate

Notes: Percentages are based on total daily energy. Evidence strength reflects the level of cohort/RCT support specifically for longevity outcomes: High = consistent evidence from multiple prospective cohorts and meta-analyses with mortality endpoints (Tables 1-5); Moderate = supported mainly by surrogate outcomes (sarcopenia, frailty, cardiometabolic biomarkers) and by general dietary guidance from the WHO, EFSA, Dietary Guidelines for Americans, Australian NHMRC, and Dietary Guidelines for Chinese Residents (2022), without longevity-specific trial endpoints. The fiber recommendation of 40–60 g/day for midlife adults exceeds current dietary guidelines (25–30 g/day) and represents a hypothesis-based upper range derived from preclinical high-fiber interventions rather than established guidance. Recommendations should be individualized.



Figure 6. A proposed dietary and lifestyle pyramid for longevity The pyramid integrates lifestyle and macronutrient layers, distinguishing it from the Mediterranean diet pyramid and the USDA Food Pyramid/MyPlate by (i) including a foundational lifestyle layer, (ii) ordering layers by macronutrient quality rather than recommended frequency, and (iii) being intended to be read together with the age-stratified macronutrient recommendations in Table 6. Layers from base to apex: lifestyle foundation (water intake, sufficient sleep, circadian regulation, physical activity, stress management, and social connection); whole-grain foods (whole grains, oats, brown rice as primary carbohydrate and fiber sources); vegetable powerhouse (diverse vegetables for micronutrient and phytochemical support); polyphenol-rich fruits (whole fruits rich in antioxidants and fiber); high-quality protein (fish, seafood, eggs, lean poultry; limited red and processed meat); healthy fat layer (olive oil, avocado, nuts, fatty fish in moderation).

should restrict claims to surrogate biomarkers.

Understudied populations: Three populations remain critically understudied. First, adults aged 75 and above, where most macronutrient trials have excluded participants by upper-age cutoff, despite this group bearing the greatest sarcopenia and multimorbidity burden. Second, populations with non-European genetic ancestry, where nutrient-pathway gene variants (e.g., MTHFR, APOE, FADS1/2) modify dietary response. Third, low- and middle-income country populations facing dual burdens of undernutrition and chronic disease. Dedicated cohorts and intervention trials in these populations are required before global longevity nutrition guidance can be considered evidence-based.

Artificial intelligence and wearable-integrated diet design: Recent advances in machine learning enable individualized diet design from baseline phenotypic and multi-omics data. Algorithms trained on CGM, microbiome, and lifestyle data already outperform standardized recommendations for glycemic control,¹⁴³⁻¹⁴⁴ and similar approaches are being extended to lipid response, satiety prediction, and adherence modeling. Continuous physiological monitoring through wearable devices (CGM, heart-rate variability, sleep, activity) provides feedback at temporal resolutions previously available only in metabolic-ward studies, enabling closed-loop dietary adjustment. The next decade will require rigorous evaluation of whether AI-guided and wearable-integrated personalized recommendations produce better long-term healthspan outcomes than expert-derived population recommendations.

Conserved molecular mechanisms in shorter-lived models: Despite the limitations of cross-species translation discussed above, model organisms (yeast, *C. elegans*, *Drosophila*) remain indispensable for mechanistic dissection of nutrient-sensing pathways, especially through high-throughput longevity screening platforms capable of testing thousands of candidate dietary factors. Coupled with humanized mouse models and emerging gene-edited minipigs, these systems will continue to identify and characterize nutritional factors capable of extending healthspan.

CONCLUSION

Macronutrient composition exerts powerful effects on lifespan and healthspan that are largely independent of total caloric intake, with the type, quality, and source of carbohydrates, proteins, fats, and dietary fiber emerging as central determinants of longevity. Diet is one of several modifiable contributors to healthy aging, operating alongside physical activity, sleep, social engagement, and avoidance of harmful exposures. Within the dietary domain, the precise regulation of macronutrient composition appears to deliver substantial longevity benefits without the practical difficulties of severe dietary restriction. Establishing healthy dietary behaviors early in life and adjusting them across the life course remains essential. The longevity diet should be regarded as a flexible, adaptable framework that varies according to individual characteristics and life stage, and that integrates the interactive effects of macronutrients, micronutrients, the microbiome, and meal timing. Rigorous long-term randomized trials incorporating biological age clocks, multi-omics endpoints, and stratification by sex and genetic background will be needed before precision nutrition recommendations can be made with the same confidence as recommendations for tobacco avoidance or physical activity. The frameworks proposed here are intended as testable hypotheses to guide that next generation of trials.

REFERENCES

- Zhang Z. D., Milman S., Lin J. R., et al. (2020). Genetics of extreme human longevity to guide drug discovery for healthy ageing. *Nat. Metab.* **2**:663–672. DOI:10.1038/s42255-020-0247-0
- Partridge L., Deelen J., and Slagboom P. E. (2018). Facing up to the global challenges of ageing. *Nature* **561**:45–56. DOI:10.1038/s41586-018-0457-8
- Barnett K., Mercer S. W., Norbury M., et al. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet* **380**:37–43. DOI:10.1016/S0140-6736(12)60240-2
- Skou S. T., Mair F. S., Fortin M., et al. (2022). Multimorbidity. *Nat. Rev. Dis. Primers* **8**:48. DOI:10.1038/s41572-022-00376-4
- Di Francesco A., Deighan A. G., Litichevskiy L., et al. (2024). Dietary restriction impacts health and lifespan of genetically diverse mice. *Nature* **634**:684–692. DOI:10.1038/s41586-024-08026-3
- McCay C. M., Crowell M. F. and Maynard L. A. (1935). The effect of retarded growth upon the length of life span and upon the ultimate body size. *J. Nutr.* **10**:63–79. DOI:10.1093/jn/10.1.63
- Schmauck-Medina T., Lautrup S., Di Francesco A., et al. (2026). Dietary restriction in aging and longevity. *Nat. Aging* **6**:485–505. DOI:10.1038/s43587-026-01091-5
- Angelidi A. M., Stefanakis K., Chou S. H., et al. (2024). Relative energy deficiency in sport (REDs): Endocrine manifestations, pathophysiology and treatments. *Endocr. Rev.* **45**:676–708. DOI:10.1210/endrev/bnae011
- Solon-Biet S. M., McMahon A. C., Ballard J. W. O., et al. (2014). The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab.* **19**:418–430. DOI:10.1016/j.cmet.2014.02.009
- Lin S. J., Kaeberlein M., Andalis A. A., et al. (2002). Calorie restriction extends *Saccharomyces cerevisiae* lifespan by increasing respiration. *Nature* **418**:344–348. DOI:10.1038/nature00829
- Lakowski B. and Hekimi S. (1998). The genetics of caloric restriction in *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. U. S. A.* **95**:13091–13096. DOI:10.1073/pnas.95.22.13091
- Partridge L., Piper M. D., and Mair W. (2005). Dietary restriction in *Drosophila*. *Mech. Ageing Dev.* **126**:938–950. DOI:10.1016/j.mad.2005.03.023
- Heymsfield S. B. and Shapses S. A. (2024). Guidance on energy and macronutrients across the life span. *N. Engl. J. Med.* **390**:1299–1310. DOI:10.1056/NEJMr2214275
- López-Otin C., Blasco M. A., Partridge L., et al. (2023). Hallmarks of aging: An expanding universe. *Cell* **186**:243–278. DOI:10.1016/j.cell.2022.11.001
- López-Otin C., Blasco M. A., Partridge L., et al. (2013). The hallmarks of aging. *Cell* **153**:1194–1217. DOI:10.1016/j.cell.2013.05.039
- Dehghan M., Mente A., Zhang X., et al. (2017). Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): A prospective cohort study. *Lancet* **390**:2050–2062. DOI:10.1016/S0140-6736(17)32252-3
- Seidemann S. B., Claggett B., Cheng S., et al. (2018). Dietary carbohydrate intake and mortality: A prospective cohort study and meta-analysis. *Lancet Public Health* **3**:e419–e428. DOI:10.1016/S2468-2667(18)30135-X
- Ardissone Korat A. V., Duscova E., Shea M. K., et al. (2025). Dietary carbohydrate intake, carbohydrate quality, and healthy aging in women. *JAMA Netw. Open* **8**:e2511056. DOI:10.1001/jamanetworkopen.2025.11056
- Khan J., Pernicova I., Nisar K., et al. (2023). Mechanisms of ageing: growth hormone, dietary restriction, and metformin. *Lancet Diabetes Endocrinol.* **11**:261–281. DOI:10.1016/S2213-8587(23)00001-3
- González A., Hall M. N., Lin S. C., et al. (2020). AMPK and TOR: The yin and yang of cellular nutrient sensing and growth control. *Cell Metab.* **31**:472–492. DOI:10.1016/j.cmet.2020.01.015
- Burkewitz K., Zhang Y., and Mair W. B. (2014). AMPK at the nexus of energetics and aging. *Cell Metab.* **20**:10–25. DOI:10.1016/j.cmet.2014.03.002
- Green C. L., Lamming D. W., and Fontana L. (2022). Molecular mechanisms of dietary restriction promoting health and longevity. *Nat. Rev. Mol. Cell Biol.* **23**:56–73. DOI:10.1038/s41580-021-00411-4
- Fung T. T., van Dam R. M., Hankinson S. E., et al. (2010). Low-carbohydrate diets and all-cause and cause-specific mortality: two cohort studies. *Ann. Intern. Med.* **153**:289–298. DOI:10.7326/0003-4819-153-5-201009070-00003
- Mazidi M., Katsiki N., Mikhailidis D. P., et al. (2019). Lower carbohydrate diets and all-cause and cause-specific mortality: A population-based cohort study and pooling of prospective studies. *Eur. Heart J.* **40**:2870–2879. DOI:10.1093/eurheartj/ehz174
- Ho F. K., Gray S. R., Welsh P., et al. (2020). Associations of fat and carbohydrate intake with cardiovascular disease and mortality: prospective cohort study of UK Biobank participants. *BMJ* **368**:m688. DOI:10.1136/bmj.m688
- Kwon Y. J., Lee H. S., Park J. Y., et al. (2020). Associating intake proportion of carbohydrate, fat, and protein with all-cause mortality in Korean adults. *Nutrients* **12**:3208. DOI:10.3390/nu12103208
- Shan Z., Guo Y., Hu F. B., et al. (2020). Association of low-carbohydrate and low-fat diets with mortality among US adults. *JAMA Intern. Med.* **180**:513–523. DOI:10.1001/jamainternmed.2019.6980
- Akter S., Mizoue T., Nanri A., et al. (2021). Low carbohydrate diet and all cause and cause-specific mortality. *Clin. Nutr.* **40**:2016–2024. DOI:10.1016/j.clnu.2020.09.022
- Ghorbani Z., Kazemi A., Shoaibinobarian N., et al. (2023). Overall, plant-based, or animal-based low carbohydrate diets and all-cause and cause-specific mortality: A systematic review and dose-response meta-analysis of prospective cohort studies. *Ageing Res. Rev.* **90**:101997. DOI:10.1016/j.arr.2023.101997
- Tamura T., Wakai K., Kato Y., et al. (2023). Dietary carbohydrate and fat intakes and risk of mortality in the Japanese population: The Japan multi-institutional collaborative cohort study. *J. Nutr.* **153**:2352–2368. DOI:10.1016/j.tjnut.2023.06.001
- Park Y. H., Lee H. S., Yang J., et al. (2024). Difference in association of carbohydrate intake with all-cause mortality between middle-aged and older Korean adults with and without diabetes mellitus: A prospective study. *Clin. Nutr.* **43**:1117–1124. DOI:10.1016/j.clnu.2024.03.024
- Cho H. J., Shin W. K., Song Y., et al. (2026). A reverse J-shaped association between carbohydrate intake and mortality among populations with high carbohydrate diets. *Clin. Nutr.* **57**:106549. DOI:10.1016/j.clnu.2025.106549
- Roberts M. N., Wallace M. A., Tomilov A. A., et al. (2017). A ketogenic diet extends

- longevity and healthspan in adult mice. *Cell Metab.* **26**:539–546.e5. DOI:10.1016/j.cmet.2017.08.005
34. Rajendran J., Tomašić N., Kotarsky H., et al. (2016). Effect of high-carbohydrate diet on plasma metabolome in mice with mitochondrial respiratory chain complex III deficiency. *Int. J. Mol. Sci.* **17**:1824. DOI:10.3390/ijms17111824
35. Ruff J. S., Hugentobler S. A., Suchy A. K., et al. (2015). Compared to sucrose, previous consumption of fructose and glucose monosaccharides reduces survival and fitness of female mice. *J. Nutr.* **145**:434–441. DOI:10.3945/jn.114.202531
36. Yang K., Hou R., Zhao J., et al. (2023). Lifestyle effects on aging and CVD: A spotlight on the nutrient-sensing network. *Ageing Res. Rev.* **92**:102121. DOI:10.1016/j.arr.2023.102121
37. Nankervis S. A., Mitchell J. M., Charchar F. J., et al. (2013). Consumption of a low glycaemic index diet in late life extends lifespan of Balb/c mice with differential effects on DNA damage. *Longev. Healthspan* **24**. DOI:10.1186/2046-2395-2-4
38. Garber A., Csizmadia I., Friedenreich C. M., et al. (2018). Association between glycemic load and cognitive function in community-dwelling older adults: Results from the brain in motion study. *Clin. Nutr.* **37**:1690–1699 DOI:10.1016/j.clnu.2017.07.011
39. Solon-Biet S. M., Cogger V. C., Pulpitel T., et al. (2019). Branched-chain amino acids impact health and lifespan indirectly via amino acid balance and appetite control. *Nat. Metab.* **1**:532–545. DOI:10.1038/s42255-019-0059-2
40. Hill C. M., Berthoud H. R., Münzberg H., et al. (2018). Homeostatic sensing of dietary protein restriction: A case for FGF21. *Front. Neuroendocrinol.* **51**:125–131. DOI:10.1016/j.yfrne.2018.06.002
41. Wilson K. A., Chamoli M., Hilsabeck T. A., et al. (2021). Evaluating the beneficial effects of dietary restrictions: A framework for precision nutrigenoscience. *Cell Metab.* **33**:2142–2173. DOI:10.1016/j.cmet.2021.08.018
42. Levine M. E., Suarez J. A., Brandhorst S., et al. (2014). Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. *Cell Metab.* **19**:407–417. DOI:10.1016/j.cmet.2014.02.006
43. Song M., Fung T. T., Hu F. B., et al. (2016). Association of animal and plant protein intake with all-cause and cause-specific mortality. *JAMA Intern. Med.* **176**:1453–1463. DOI:10.1001/jamainternmed.2016.4182
44. Budhathoki S., Sawada N., Iwasaki M., et al. (2019). Association of animal and plant protein intake with all-cause and cause-specific mortality in a Japanese cohort. *JAMA Intern. Med.* **179**:1509–1518. DOI:10.1001/jamainternmed.2019.2806
45. Naghshi S., Sadeghi O., Willett W. C., et al. (2020). Dietary intake of total, animal, and plant proteins and risk of all cause, cardiovascular, and cancer mortality: Systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ* **370**:m2412. DOI:10.1136/bmj.m2412
46. Chen Z., Glisic M., Song M., et al. (2020). Dietary protein intake and all-cause and cause-specific mortality: Results from the Rotterdam Study and a meta-analysis of prospective cohort studies. *Eur. J. Epidemiol.* **35**:411–429. DOI:10.1007/s10654-020-00607-6
47. Huang J., Liao L. M., Weinstein S. J., et al. (2020). Association between plant and animal protein intake and overall mortality in the nih-aarp diet and health study. *JAMA Intern. Med.* **180**:1173–1184. DOI:10.1001/jamainternmed.2020.2790
48. Xu B., Wang M., Pu L., et al. (2021). Association of dietary intake of branched-chain amino acids with long-term risks of CVD, cancer and all-cause mortality. *Public Health Nutr.* **25**:3390–3400. DOI:10.1017/s1368980021004948
49. Hirani V., Naganathan V., Blyth F., et al. (2017). Higher protein intake and protein-energy malnutrition were associated with all-cause mortality in older men: The concord health and ageing in men project (CHAMP). *Eur. J. Clin. Nutr.* **71**:1366–1372. DOI:10.1038/ejcn.2017.69
50. Tanaka T., Tategawar S. A., Jin Y., et al. (2019). Adequate intake of protein is associated with reduced mortality risk in the very old: the kawasaki aging and wellbeing project. *J. Nutr. Health Aging* **23**:715–721. DOI:10.1007/s12603-019-1221-y
51. Wallerer S., Papakonstantinou T., Morze J., et al. (2024). Association between substituting macronutrients and all-cause mortality: a network meta-analysis of prospective observational studies. *eClinicalMedicine* **75**:102807. DOI:10.1016/j.eclim.2024.102807
52. Papanikolaou Y., Phillips S., and Fulgoni V. (2025). Animal and plant protein usual intakes are not adversely associated with all-cause, cardiovascular disease-, or cancer-related mortality risk: An NHANES III analysis. *Appl. Physiol. Nutr. Metab.* **50**:1–8. DOI:10.1139/apnm-2024-0124
53. Orentreich N., Matias J. R., DeFelice A., et al. (1993). Low methionine ingestion by rats extends life span. *J. Nutr.* **123**:269–274. DOI:10.1093/jn/123.2.269
54. Miller R. A., Buehner G., Chang Y., et al. (2005). Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. *Aging Cell* **4**:119–125. DOI:10.1111/j.1474-9726.2005.00152.x
55. Hernández-Arciga U., Stamenkovic C., Yadav S., et al. (2025). Dietary methionine restriction started late in life promotes healthy aging in a sex-specific manner. *Sci. Adv.* **11**:eads1532. DOI:10.1126/sciadv.ads1532
56. Bárcena C., Quirós P. M., Durand S., et al. (2018). Methionine restriction extends lifespan in progeroid mice and alters lipid and bile acid metabolism. *Cell Rep.* **24**:2392–2403. DOI:10.1016/j.celrep.2018.07.089
57. De Marte M. L. and Enesco H. E. (1986). Influence of low tryptophan diet on survival and organ growth in mice. *Mech. Ageing Dev.* **36**:161–171. DOI:10.1016/0047-6374(86)90017-5
58. Brind J., Malloy V., Augie I., et al. (2011). Dietary glycine supplementation mimics lifespan extension by dietary methionine restriction in Fisher 344 rats. *FASEB J.* **25**:528.2. DOI:10.1096/fasebj.25.1.supplement.528.2
59. Miller R. A., Harrison D. E., Astle C. M., et al. (2019). Glycine supplementation extends lifespan of male and female mice. *Aging Cell* **18**:e12953. DOI:10.1111/accel.12953
60. Hafidi M., Pérez I., Zamora J., et al. (2004). Glycine intake decreases plasma free fatty acids, adipose cell size, and blood pressure in sucrose-fed rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **287**:R1387–R1393. DOI:10.1152/ajpregu.00159.2004
61. Cruz M., Maldonado-Bernal C., Mondragón-González R., et al. (2008). Glycine treatment decreases proinflammatory cytokines and increases interferon-γ in patients with Type 2 diabetes. *J. Endocrinol. Invest.* **31**:694–699. DOI:10.1007/BF03346417
62. D'Antona G., Ragni M., Cardile A., et al. (2010). Branched-chain amino acid supplementation promotes survival and supports cardiac and skeletal muscle mitochondrial biogenesis in middle-aged mice. *Cell Metab.* **12**:362–372. DOI:10.1016/j.cmet.2010.08.016
63. Green C. L., Trautman M. E., Chaiyakul K., et al. (2023). Dietary restriction of isoleucine increases healthspan and lifespan of genetically heterogeneous mice. *Cell Metab.* **35**:1976–1995.e6. DOI:10.1016/j.cmet.2023.10.005
64. Mirzaei H., Suarez J. A., and Longo V. D. (2014). Protein and amino acid restriction, aging and disease: from yeast to humans. *Trends Endocrinol. Metab.* **25**:558–566. DOI:10.1016/j.tem.2014.07.002
65. Mutlu A. S., Duffy J., and Wang M. C. (2021). Lipid metabolism and lipid signals in aging and longevity. *Dev. Cell* **56**:1394–1407. DOI:10.1016/j.devcl.2021.03.034
66. Berryman D. E., Christiansen J. S., Johannsson G., et al. (2008). Role of the GH/IGF-1 axis in lifespan and healthspan: lessons from animal models. *Growth Horm. IGF Res.* **18**:455–471. DOI:10.1016/j.ghir.2008.05.005
67. Global BMI Mortality Collaboration. (2016). Body-mass index and all-cause mortality: Individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* **388**:776–786. DOI:10.1016/S0140-6736(16)30175-1
68. Powell-Wiley T. M., Poirier P., Burke L. E., et al. (2021). Obesity and cardiovascular disease: A scientific statement from the American heart association. *Circulation* **143**:e984–e1010. DOI:10.1161/CIR.0000000000000973
69. Wang D. D., Li Y., Chiuve S. E., et al. (2016). Association of specific dietary fats with total and cause-specific mortality. *JAMA Intern. Med.* **176**:1134–1145. DOI:10.1001/jamainternmed.2016.2417
70. Zhuang P., Zhang Y., He W., et al. (2019). Dietary fats in relation to total and cause-specific mortality in a prospective cohort of 521 120 individuals with 16 years of follow-up. *Circ. Res.* **124**:757–768. DOI:10.1161/CIRCRESAHA.118.314038
71. Mazidi M., Mikhailidis D. P., Sattar N., et al. (2020). Association of types of dietary fats and all-cause and cause-specific mortality: A prospective cohort study and meta-analysis of prospective studies with 1,164,029 participants. *Clin. Nutr.* **39**:3677–3686. DOI:10.1016/j.clnu.2020.03.028
72. Kim Y., Je Y., and Giovannucci E. L. (2021). Association between dietary fat intake and mortality from all-causes, cardiovascular disease, and cancer: A systematic review and meta-analysis of prospective cohort studies. *Clin. Nutr.* **40**:1060–1070. DOI:10.1016/j.clnu.2020.07.007
73. Zhao B., Gan L., Graubard B. I., et al. (2024). Plant and animal fat intake and overall and cardiovascular disease mortality. *JAMA Intern. Med.* **184**:1234–1245. DOI:10.1001/jamainternmed.2024.3799
74. Kennedy B. S., Richeson R. P., and Houde A. J. (2025). Saturated fatty acid intake and all-cause mortality: Chain length matters. *Precis. Nutr.* **4**:e00108. DOI:10.1097/PN9.0000000000000108
75. Liu Y., Gu X., Li Y., et al. (2025). Changes in fatty acid intake and subsequent risk of all-cause and cause-specific mortality in males and females: A prospective cohort study. *Am. J. Clin. Nutr.* **121**:141–150. DOI:10.1016/j.ajcnut.2024.11.012
76. Ma Y., Zheng Z., Zhuang L., et al. (2024). Dietary macronutrient intake and cardiovascular disease risk and mortality: A systematic review and dose-response meta-analysis of prospective cohort studies. *Nutrients* **16**:152. DOI:10.3390/nu16010152
77. Zhang Z., Ding L., and Liang Y., et al. (2025). The association of dietary fatty acids intake with overall and cause-specific mortality: A prospective cohort study from 1999–2018 cycles of the NHANES. *Front Nutr.* **12**:1468513. DOI:10.3389/fnut.2025.1468513
78. Shi D., Han T., Chu X., et al. (2021). An isocaloric moderately high-fat diet extends lifespan in male rats and *Drosophila*. *Cell Metab.* **33**:581–597.e9. DOI:10.1016/j.cmet.2020.12.017
79. Dalderup L. M. and Visser W. (1971). Influence of extra sucrose, fats, protein and of cyclamate in daily food on life-span of rats. *Experientia* **27**:519–521. DOI:10.1007/BF02147574
80. Harris W. S., Tintle N. L., Imamura F., et al. (2021). Blood n-3 fatty acid levels and total and cause-specific mortality from 17 prospective studies. *Nat. Commun.* **12**:2329. DOI:10.1038/s41467-021-22370-2
81. Moore T. D., Martin-Creuzburg D., and Yampolsky L. Y. (2023). Diet effects on longevity, heat tolerance, lipid peroxidation and mitochondrial membrane potential

- in. *Daphnia*. *Oecologia* **202**:151–163. DOI:10.1007/s00442-023-05382-1
82. O'Rourke E. J., Kuballa P., Xavier R., et al. (2013). ω -6 Polyunsaturated fatty acids extend life span through the activation of autophagy. *Genes Dev.* **27**:429–440. DOI:10.1101/gad.205294.112
83. Nehra D., Le H. D., Fallon E. M., et al. (2012). Prolonging the female reproductive lifespan and improving egg quality with dietary omega-3 fatty acids. *Aging Cell* **11**:1046–1054. DOI:10.1111/accel.12006
84. Honda Y., Fujita Y., Maruyama H., et al. (2011). Lifespan-extending effects of royal jelly and its related substances on the nematode *Caenorhabditis elegans*. *PLoS One* **6**:e23527. DOI:10.1371/journal.pone.0023527
85. Johnson A. A. and Stolzing A. (2019). The role of lipid metabolism in aging, lifespan regulation, and age-related disease. *Aging Cell* **18**:e13048. DOI:10.1111/accel.13048
86. Han S., Schroeder E. A., Silva-Garcia C. G., et al. (2017). Mono-unsaturated fatty acids link H3K4me3 modifiers to *C. elegans* lifespan. *Nature* **544**:185–190. DOI:10.1038/nature21686
87. Hulbert A. J. (2011). Longevity, lipids and *C. elegans*. *Aging (Albany NY)* **3**:81–82. DOI:10.18632/aging.100288
88. Streeper R. S., Grueter C. A., Salomonis N., et al. (2012). Deficiency of the lipid synthesis enzyme, DGAT1, extends longevity in mice. *Aging (Albany NY)* **4**:13–27. DOI:10.18632/aging.100424
89. Harrison D. E., Strong R., Allison D. B., et al. (2014). Acarbose, 17- α -estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males. *Aging Cell* **13**:273–282. DOI:10.1111/accel.12170
90. Blüher M. (2008). Fat tissue and long life. *Obes. Facts* **1**:176–182. DOI:10.1159/000145930
91. Darcy J., McFadden S., and Bartke A. (2017). Altered structure and function of adipose tissue in long-lived mice with growth hormone-related mutations. *Adipocyte* **6**:69–75. DOI:10.1080/21623945.2017.1308990
92. Liao C. Y., Rikke B. A., Johnson T. E., et al. (2011). Fat maintenance is a predictor of the murine lifespan response to dietary restriction. *Aging Cell* **10**:629–639. DOI:10.1111/j.1474-9726.2011.00702.x
93. Muzumdar R., Allison D. B., Huffman D. M., et al. (2008). Visceral adipose tissue modulates mammalian longevity. *Aging Cell* **7**:438–440. DOI:10.1111/j.1474-9726.2008.00391.x
94. Silberberg M. and Silberberg R. (1954). Factors modifying the lifespan of mice. *Am. J. Physiol.* **177**:23–26. DOI:10.1152/ajplegacy.1954.177.1.23
95. Li J., Lin Y. C., Zuo H. L., et al. (2025). Dietary omega-3 PUFAS in metabolic disease research: A decade of omics-enabled insights (2014–2024). *Nutrients* **17**:1836. DOI:10.3390/nu17111836
96. Sacks F. M., Lichtenstein A. H., Wu J. H. Y., et al. (2017). Dietary fats and cardiovascular disease: a presidential advisory from the american heart association. *Circulation* **136**:e1–e23. DOI:10.1161/CIR.0000000000000510
97. Slavin J. L. (2005). Dietary fiber and body weight. *Nutrition* **21**:411–418. DOI:10.1016/j.nut.2004.08.018
98. Park Y., Subar A. F., Hollenbeck A., et al. (2011). Dietary fiber intake and mortality in the NIH-AARP diet and health study. *Arch. Intern. Med.* **171**:1061–1068. DOI:10.1001/archinternmed.2011.18
99. Kim Y. and Je Y. (2014). Dietary fibre intake and mortality from cardiovascular disease and all cancers: A meta-analysis of prospective cohort studies. *Arch. Cardiovasc. Dis.* **107**:622–633. DOI:10.1016/j.acvd.2014.10.001
100. Yang Y., Zhao L. G., Wu Q. J., et al. (2015). Association between dietary fiber and lower risk of all-cause mortality: a meta-analysis of cohort studies. *Am. J. Epidemiol.* **181**:83–91. DOI:10.1093/aje/kwu257
101. Veronese N., Solmi M., Caruso M. G., et al. (2018). Dietary fiber and health outcomes: An umbrella review of systematic reviews and meta-analyses. *Am. J. Clin. Nutr.* **107**:436–444. DOI:10.1093/ajcn/nqx082
102. Katagiri R., Goto A., Sawada N., et al. (2020). Dietary fiber intake and total and cause-specific mortality: The Japan public health center-based prospective study. *Am. J. Clin. Nutr.* **111**:1027–1035. DOI:10.1093/ajcn/nqaa002
103. Kwon Y. J., Lee H. S., Park G., et al. (2022). Association of dietary fiber intake with all-cause mortality and cardiovascular disease mortality: A 10-year prospective cohort study. *Nutrients* **14**:3089. DOI:10.3390/nu14153089
104. Mirrafiei A., Jayedi A., and Shab-Bidar S. (2023). Total and different dietary fiber subtypes and the risk of all-cause, cardiovascular, and cancer mortality: A dose-response meta-analysis of prospective cohort studies. *Food Funct.* **14**:10667–10680. DOI:10.1039/d3fo03143h
105. Ramezani F., Pourghazi F., Eslami M., et al. (2024). Dietary fiber intake and all-cause and cause-specific mortality: An updated systematic review and meta-analysis of prospective cohort studies. *Clin. Nutr.* **43**:65–83. DOI:10.1016/j.clnu.2023.11.005
106. Reynolds A., Mann J., Cummings J., et al. (2019). Carbohydrate quality and human health: A series of systematic reviews and meta-analyses. *Lancet* **393**:434–445. DOI:10.1016/S0140-6736(18)31809-9
107. Guo Y., Li M., and Huang Y. (2025). Association of dietary fiber intake with all-cause and cardiovascular mortality in U. S. adults with metabolic syndrome. *Front. Nutr.* **12**:1659000. DOI:10.3389/fnut.2025.1659000
108. Beghelli D., Giusti L., Zallocco L., et al. (2024). Dietary fiber supplementation increases *Drosophila melanogaster* lifespan and gut microbiota diversity. *Food Funct.* **15**:7468–7477. DOI:10.1039/d4fo00879k
109. Dong Y., Sun H., Yang W., et al. (2019). The effect of inulin on lifespan, related gene expression and gut microbiota in InR p5545/TM3 mutant *Drosophila melanogaster*. *Nutrients* **11**:636. DOI:10.3390/nu11030636
110. Hu F., Yu L., Tu X., et al. (2025). A high-fiber diet mimics aging-related signatures of caloric restriction in mammals. *Nat. Commun.* **16**:5917. DOI:10.1038/s41467-025-61046-z
111. Kokkonen G. C. and Barrows C. H. (1988). The effect of dietary cellulose on life-span and biochemical variables of male-mice. *Age* **11**:7–9. DOI:10.1007/BF02431758
112. Gabandé-Rodríguez E., Gómez de Las Heras M. M., Ramírez-Ruiz de Erenchun P., et al. (2026). Butyrate extends health and lifespan in mice with mitochondrial deficiency. *Nat. Commun.* **17**:3909. DOI:10.1038/s41467-026-70547-4
113. Senior A. M., Nakagawa S., Raubenheimer D., et al. (2020). Global associations between macronutrient supply and age-specific mortality. *Proc. Natl. Acad. Sci. U. S. A.* **117**:30824–30835. DOI:10.1073/pnas.2015058117
114. Senior A. M., Solon-Biet S. M., Cogger V. C., et al. (2019). Dietary macronutrient content, age-specific mortality and lifespan. *Proc. Biol. Sci.* **286**:20190393. DOI:10.1098/rspb.2019.0393
115. Solon-Biet S. M., Walters K. A., Simanainen U. K., et al. (2015). Macronutrient balance, reproductive function, and lifespan in aging mice. *Proc. Natl. Acad. Sci. U. S. A.* **112**:3481–3486. DOI:10.1073/pnas.1422041112
116. Le Couteur D. G., Solon-Biet S., Cogger V. C., et al. (2016). The impact of low-protein high-carbohydrate diets on aging and lifespan. *Cell. Mol. Life Sci.* **73**:1237–1252. DOI:10.1007/s00018-015-2120-y
117. Rapkin J., Archer C. R., Grant C. E., et al. (2017). Little evidence for intralocus sexual conflict over the optimal intake of nutrients for life span and reproduction in the black field cricket *Teleogryllus commodus*. *Evolution* **71**:2159–2177. DOI:10.1111/evo.13299
118. Simpson S. J., Raubenheimer D., Cogger V. C., et al. (2018). The nutritional geometry of liver disease including non-alcoholic fatty liver disease. *J. Hepatol.* **68**:316–325. DOI:10.1016/j.jhep.2017.10.005
119. Simpson S. J. and Raubenheimer D. (2011). The nature of nutrition: A unifying framework. *Aust. J. Zool.* **59**:350–368. DOI:10.1071/ZO11068
120. Buettner D. and Skemp S. (2016). Blue zones: lessons from the world's longest lived. *Am. J. Lifestyle Med.* **10**:318–321. DOI:10.1177/1559827616637066
121. Willcox D. C., Willcox B. J., Todoriki H., et al. (2009). The Okinawan diet: Health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J. Am. Coll. Nutr.* **28**:500S–516S. DOI:10.1080/07315724.2009.10718117
122. Willcox B. J. and Willcox D. C. (2014). Caloric restriction, caloric restriction mimetics, and healthy aging in Okinawa: Controversies and clinical implications. *Curr. Opin. Clin. Nutr. Metab. Care* **17**:51–58. DOI:10.1097/MCO.0000000000000019
123. Duan H., Li J., Yu L., et al. (2024). The road ahead of dietary restriction on anti-aging: Focusing on personalized nutrition. *Crit. Rev. Food Sci. Nutr.* **64**:891–908. DOI:10.1080/10408398.2022.2110034
124. Soltani S., Jayedi A., Shab-Bidar S., et al. (2019). Adherence to the Mediterranean diet in relation to all-cause mortality: A systematic review and dose-response meta-analysis of prospective cohort studies. *Adv. Nutr.* **10**:1029–1039. DOI:10.1093/advances/nmz041
125. Soltani S., Arablou T., Jayedi A., et al. (2020). Adherence to the dietary approaches to stop hypertension (DASH) diet in relation to all-cause and cause-specific mortality: A systematic review and dose-response meta-analysis of prospective cohort studies. *Nutr. J.* **19**:37. DOI:10.1186/s12937-020-00554-8
126. English L. K., Ard J. D., Bailey R. L., et al. (2021). Evaluation of dietary patterns and all-cause mortality: A systematic review. *JAMA Netw. Open* **4**:e2122277. DOI:10.1001/jamanetworkopen.2021.22277
127. Matsuyama S., Sawada N., Tomata Y., et al. (2021). Association between adherence to the Japanese diet and all-cause and cause-specific mortality: The Japan public health center-based prospective study. *Eur. J. Nutr.* **60**:1327–1336. DOI:10.1007/s00394-020-02330-0
128. Ahmad S., Moorthy M. V., Lee I. M., et al. (2024). Mediterranean diet adherence and risk of all-cause mortality in women. *JAMA Netw. Open* **7**:e2414322. DOI:10.1001/jamanetworkopen.2024.14322
129. Tan J., Zhang S., Jiang Y., et al. (2024). Plant-based diet and risk of all-cause mortality: A systematic review and meta-analysis. *Front. Nutr.* **11**:1481363. DOI:10.3389/fnut.2024.1481363
130. Karam G., Agarwal A., Sadeghirad B., et al. (2023). Comparison of seven popular structured dietary programmes and risk of mortality and major cardiovascular events in patients at increased cardiovascular risk: Systematic review and network meta-analysis. *BMJ* **380**:e072003. DOI:10.1136/bmj-2022-072003
131. Mo Q., Wu J., Lu Y., et al. (2025). Plant-based diets and total and cause-specific mortality: A meta-analysis of prospective studies. *Front. Nutr.* **12**:1518519. DOI:10.3389/fnut.2025.1518519
132. Murai U., Ishihara J., Takachi R., et al. (2025). Japanese diet index score and cause-specific mortality in Japanese men and women: The Japan public health center-based prospective study. *J. Nutr.* **155**:3726–3736. DOI:10.1016/j.tjnut.2025.09.003
133. Lăcătușu C. M., Grigorescu E. D., Floria M., et al. (2019). The Mediterranean diet: From an environment-driven food culture to an emerging medical prescription. *Int. J. Environ. Res. Public Health* **16**:942. DOI:10.3390/ijerph16060942

134. Martinez-Gonzalez M. A. and Martin-Calvo N. (2016). Mediterranean diet and life expectancy; beyond olive oil, fruits, and vegetables. *Curr. Opin. Clin. Nutr. Metab. Care* **19**:401–407. DOI:10.1097/MCO.0000000000000316
135. Dominguez L. J., Barbagallo M., Muñoz-García M., et al. (2019). Dietary patterns and cognitive decline: Key features for prevention. *Curr. Pharm. Des.* **25**:2428–2442. DOI:10.2174/1381612825666190722110458
136. Morze J., Danielewicz A., Przybyłowicz K., et al. (2021). An updated systematic review and meta-analysis on adherence to mediterranean diet and risk of cancer. *Eur. J. Nutr.* **60**:1561–1586. DOI:10.1007/s00394-020-02346-6
137. Fiorito G., Cains S., Palli D., et al. (2021). DNA methylation-based biomarkers of aging were slowed down in a two-year diet and physical activity intervention trial: The DAMA study. *Aging Cell* **20**:e13439. DOI:10.1111/ace1.13439
138. Kim Y., Huan T., Joehanes R., et al. (2022). Higher diet quality relates to decelerated epigenetic aging. *Am. J. Clin. Nutr.* **115**:163–170. DOI:10.1093/ajcn/nqab201
139. Drabińska N., Wiczowski W., and Piskula M. K. (2021). Recent advances in the application of a ketogenic diet for obesity management. *Trends Food Sci. Technol.* **110**:28–38. DOI:10.1016/j.tifs.2021.01.080
140. Wei S. J., Schell J. R., Chocron E. S., et al. (2022). Ketogenic diet induces p53-dependent cellular senescence in multiple organs. *Sci. Adv.* **10**:eado1463. DOI:10.1126/sciadv.ado1463
141. Berry S. E., Valdes A. M., Drew D. A., et al. (2020). Human postprandial responses to food and potential for precision nutrition. *Nat. Med.* **26**:964–973. DOI:10.1038/s41591-020-0934-0
142. Livingstone K. M., Ramos-Lopez O., Pérusse L., et al. (2022). Precision nutrition: A review of current approaches and future endeavours. *Trends Food Sci. Technol.* **128**:253–264. DOI:10.1016/j.tifs.2022.08.017
143. Bermingham K. M., Linenberg I., Polidori L., et al. (2024). Effects of a personalized nutrition program on cardiometabolic health: A randomized controlled trial. *Nat. Med.* **30**:1888–1897. DOI:10.1038/s41591-024-02951-6
144. Asnicar F., Berry S. E., Valdes A. M., et al. (2021). Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nat. Med.* **27**:321–332. DOI:10.1038/s41591-020-01183-8
145. Pang S., Chen X., Lu Z., et al. (2023). Longevity of centenarians is reflected by the gut microbiome with youth-associated signatures. *Nat. Aging* **3**:436–449. DOI:10.1038/s43587-023-00389-y
146. Manoogian E. N. C., Chow L. S., Taub P. R., et al. (2022). Time-restricted eating for the prevention and management of metabolic diseases. *Endocr. Rev.* **43**:405–436. DOI:10.1210/edrev/bnab027
147. Wilkinson M. J., Manoogian E. N. C., Zadourian A., et al. (2020). Ten-hour time-restricted eating reduces weight, blood pressure, and atherogenic lipids in patients with metabolic syndrome. *Cell Metab.* **31**:92–104.e5. DOI:10.1016/j.cmet.2019.11.004
148. Monteiro C. A., Cannon G., Lawrence M., et al. (2019). Ultra-processed foods, diet quality, and health using the NOVA classification system. *Rome: Food and Agriculture Organization of the United Nations (FAO)*. <https://openknowledge.fao.org/handle/20.500.14283/ca5644en>
149. Lane M. M., Gamage E., Du S., et al. (2024). Ultra-processed food exposure and adverse health outcomes: umbrella review of epidemiological meta-analyses. *BMJ* **384**:e077310. DOI:10.1136/bmj-2023-077310
150. Fang Z., Rossato S. L., Hang D., et al. (2024). Association of ultra-processed food consumption with all cause and cause specific mortality: Population based cohort study. *BMJ* **385**:e078476. DOI:10.1136/bmj-2023-078476

FUNDING AND ACKNOWLEDGMENTS

This study was supported by the National Key Research and Development Program of China (2023YFF1104204), National Natural Science Foundation of China (82171550). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors contributed to the literature search and interpretation of the available evidence. Jintao Huang drafted the manuscript, and all authors critically revised the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.