Microbiome and aging: Trajectories of microbiome age across human ecosystems and their systemic effects

Zhexin Ni[1#], Jiaojiao Xie[2#], Zhichun Zhang[3#], Keming Zhang[4#], Jie Ding[5#], Mingyang Chang[6#], Ying Su[7#], Yunan Zhang[8#], Mingfei Yao[2], Chengyuan Wang[9], Yan Yan[9], Wenjie Fang[4], Hainv Gao[10], Xuecong Tian[11], Yangshuo Li[5], Xinlin Zhu[4], Wen Zhang[12], Wanqing Liao[4], Gaoyuan Xu[13], Guojing Chen[1], Xiaoyi Lv[7*], Chaoqin Yu[5*], Weihua Pan[4*], Vadim Molodtsov[14*], Lanjuan Li[2,15*], Yue Gao[1*], Wei Zhou[1,16*]

[1]Academy of Military Medical Sciences; [2]The First Affiliated Hospital, Zhejiang University School of Medicine; [3]Department of Cariology and Endodontology, Peking University School and Hospital of Stomatology; [4]Department of Dermatology, The Second Affiliated Hospital of Naval Medical University; [5]Gynecology Department of Traditional Chinese Medicine, The First Affiliated Hospital of Naval Medical University; [6]Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine; [7]School of Computer Science and Technology, Xinjiang University; [8]Beijing University of Chinese Medicine; [9]Shanghai Institute of Materia Medica, Chinese Academy of Sciences; [10]Shulan Hangzhou Hospital, Affiliated to Shulan International Medical College, Zhejiang Shuren University; [11]Ghent University; [12]Florida Atlantic University; [13]China Medical University; [14]Peoples' Friendship University of Russia; [15]Yuhang Institute for Collaborative Innovation and Translational Research in Life Sciences and Technology; [16]Xinjiang Key Laboratory of High-Altitude Diseases and Characteristic Preparations;

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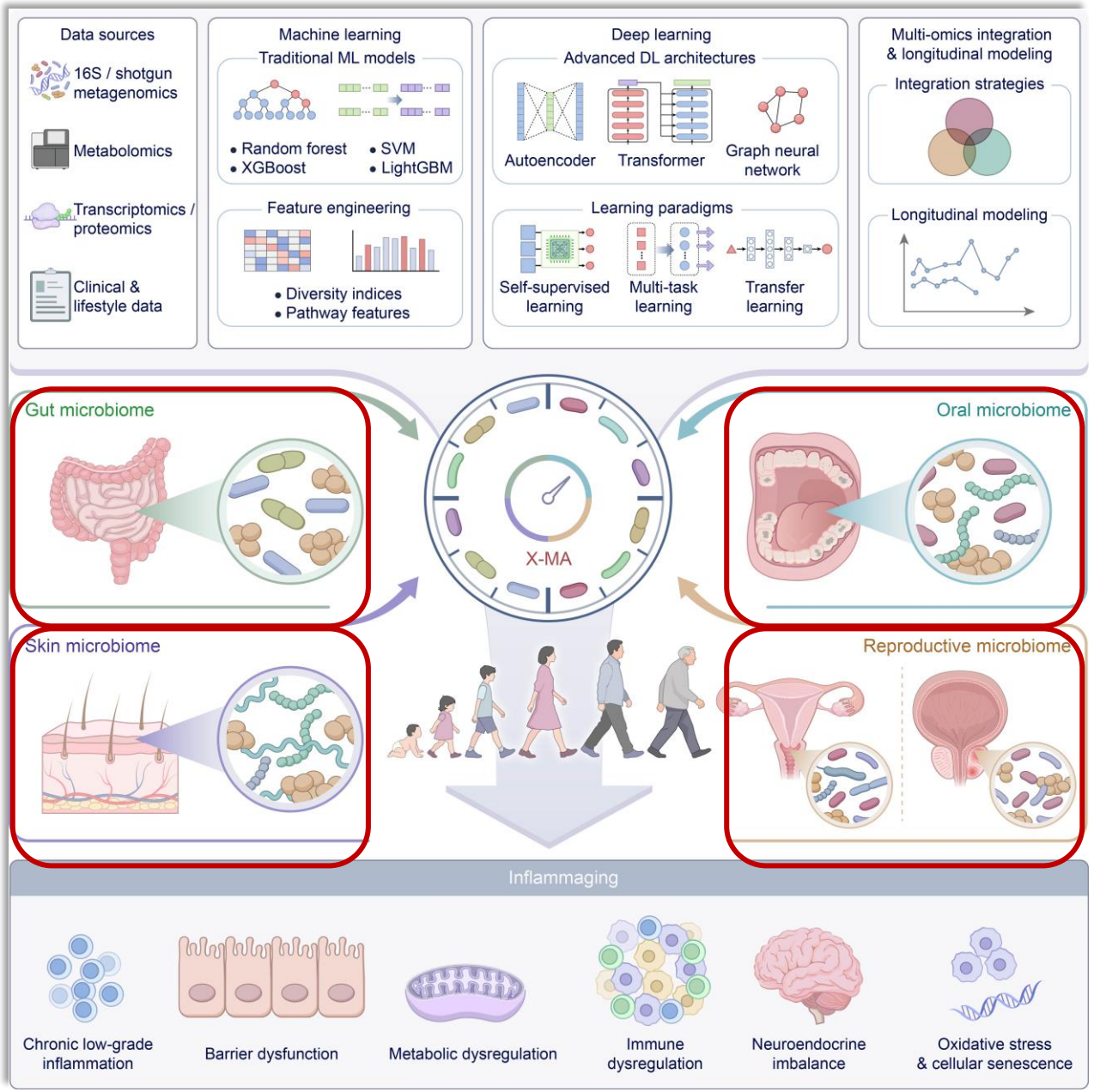
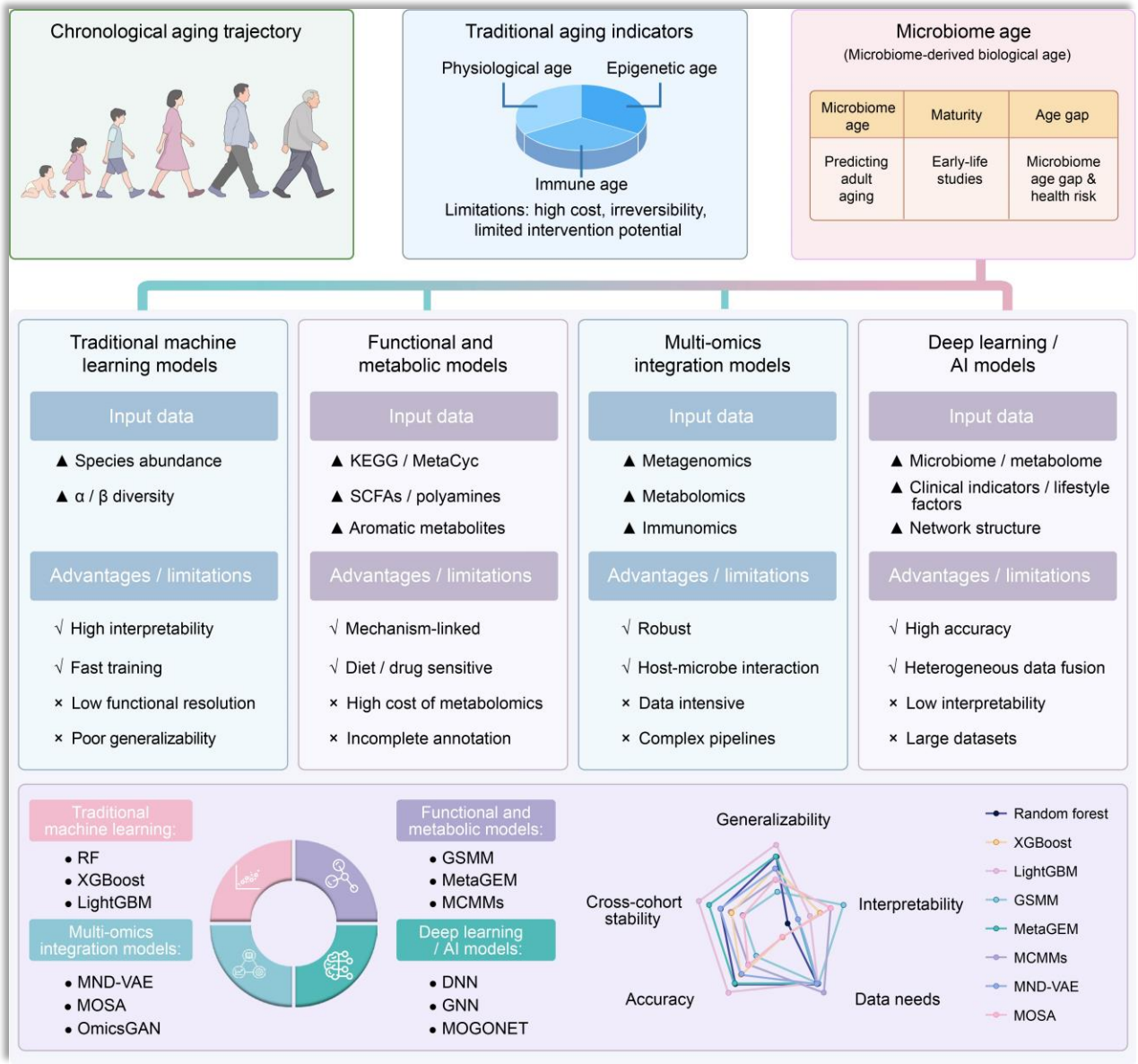
Highlights



- The microbiome age (MA) reflect host aging trajectories through dynamic alterations in microbial composition, function, and host–microbe interactions across multiple body ecosystems;
- Age-associated microbial remodeling exhibits both site-specific characteristics and convergent systemic patterns;
- MA represents a promising systems-level biomarker bridging computational prediction, microbial ecology, and aging biology, with broad implications for aging assessment, risk stratification, and precision intervention.

Conceptual framework and computational approaches for microbiome age



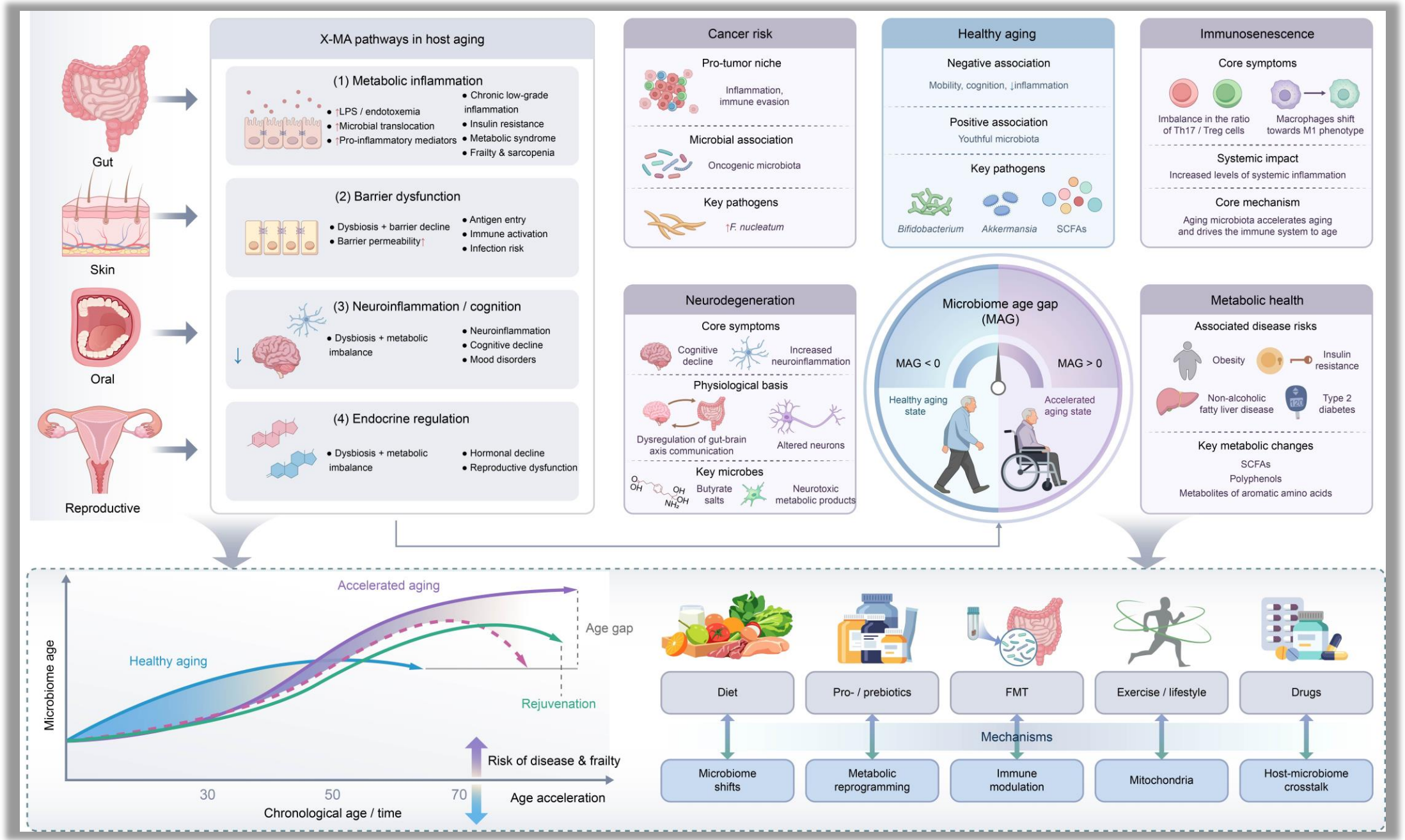
- Traditional aging biomarkers are often constrained by limited accessibility, high cost, poor dynamic responsiveness, or restricted intervention relevance;

- MA, defined as a microbiome-derived indicator of biological aging based on compositional and functional microbial features, has emerged as a promising and dynamically responsive biomarker reflecting host aging trajectories;

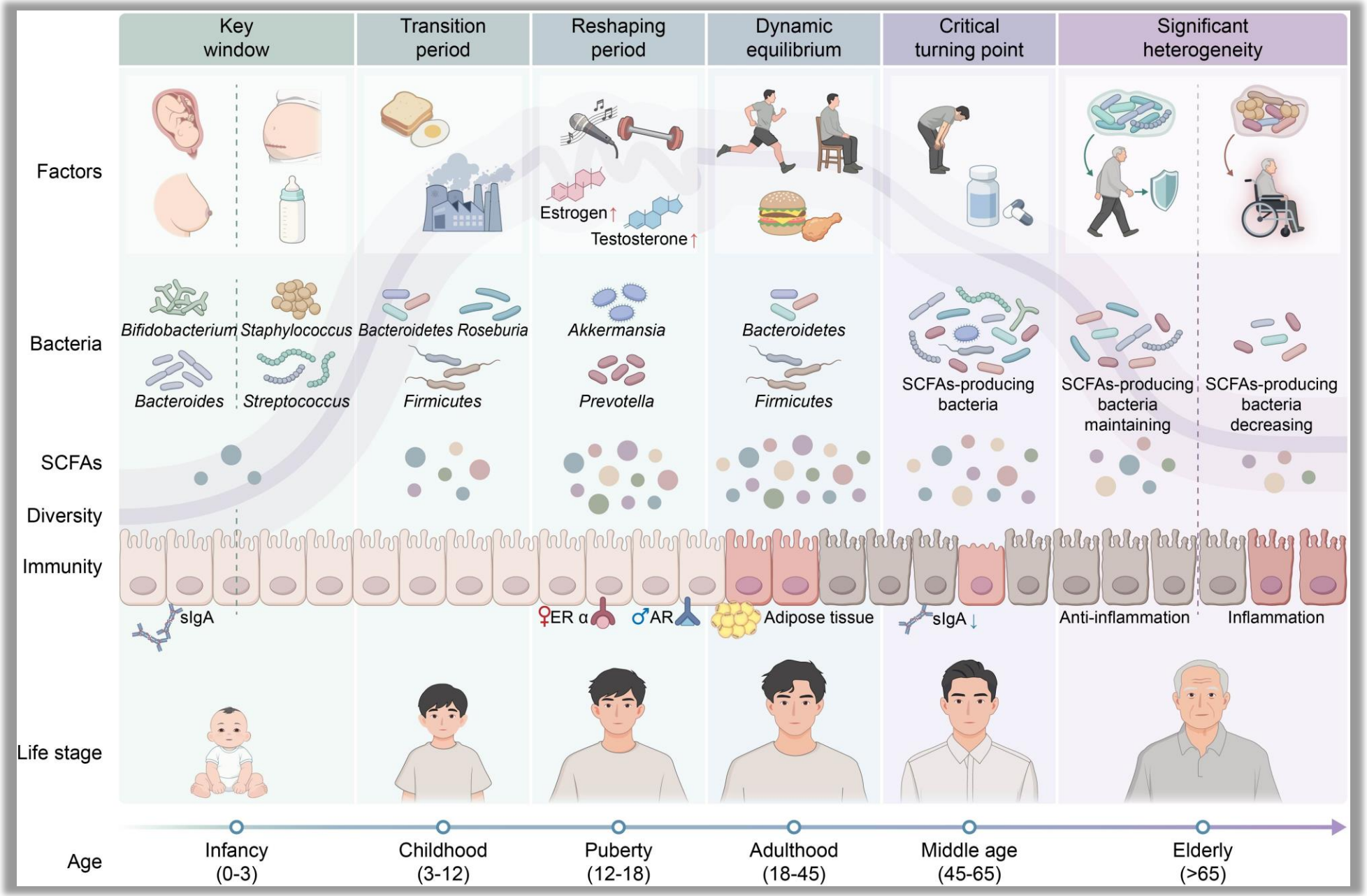
- Computational strategies for MA prediction can be broadly categorized into four major classes:

(1) traditional machine learning models;
(2) functional and metabolic models;
(3) multi-omics integration models;
(4) deep learning and artificial intelligence models.

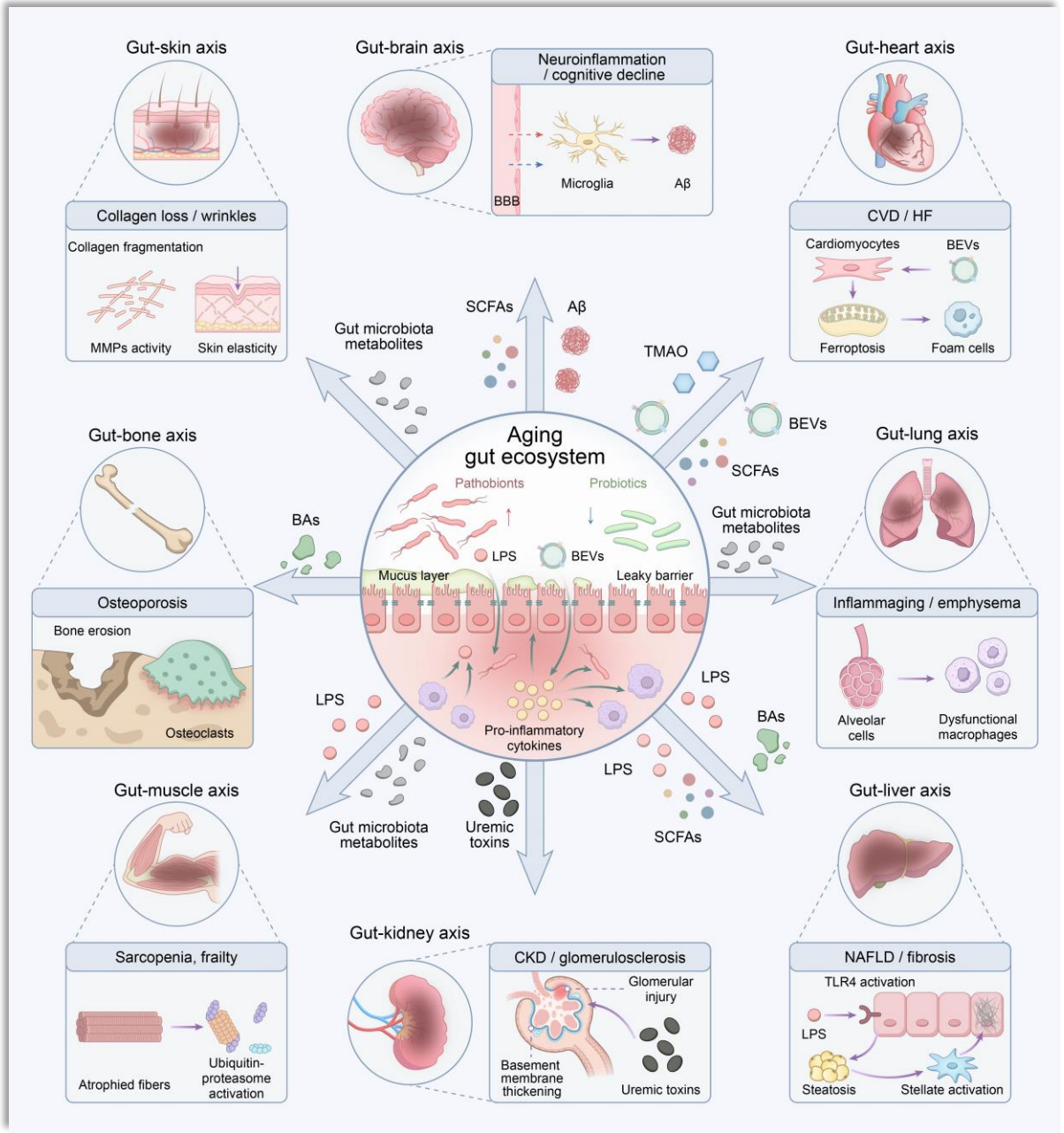
Dynamic trajectory of the microbiome age gap and its systemic health implications



Dynamic changes in gut microbiome and function across the human lifespan



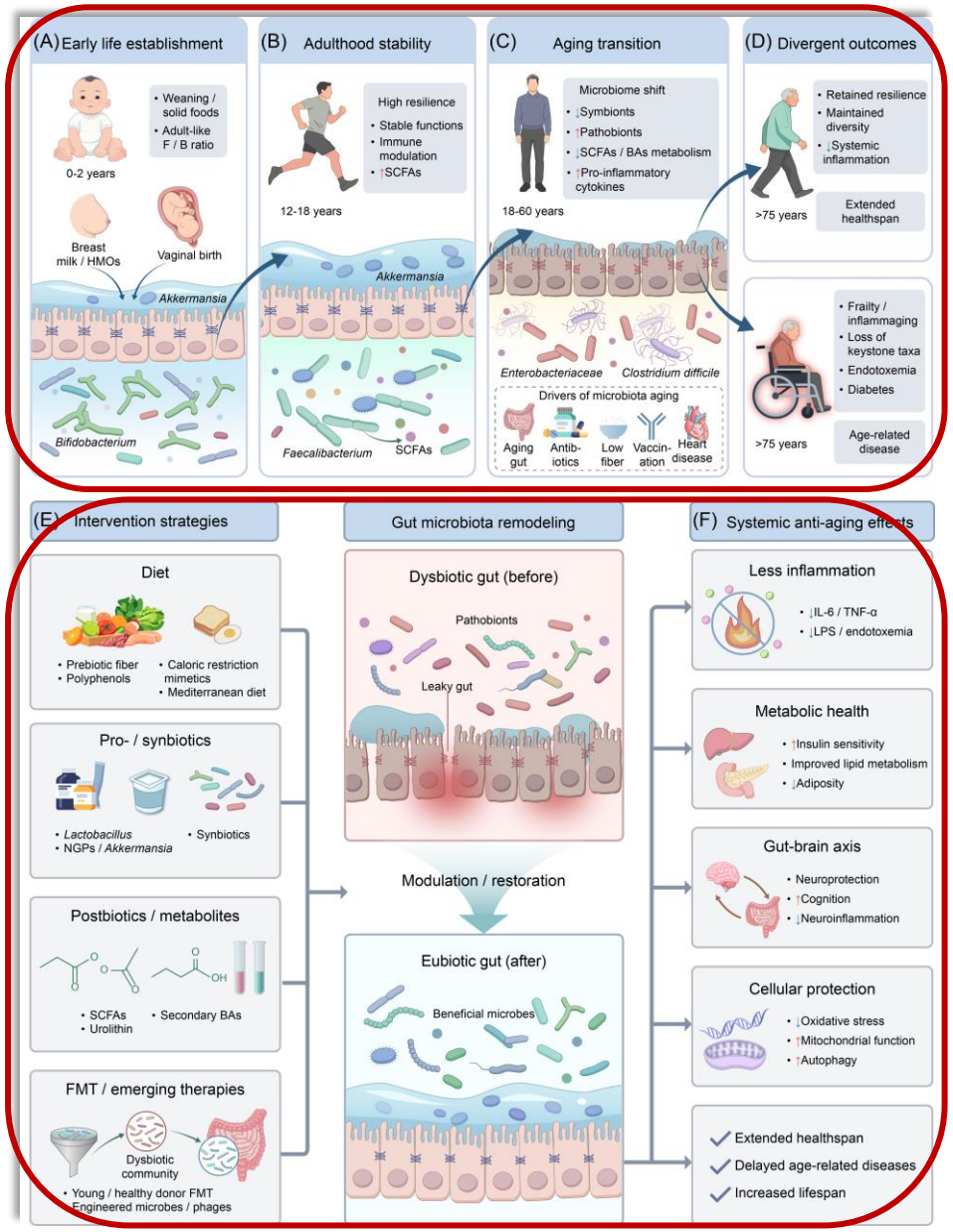
The aging gut connects with multiple organs via the “gut-X” axis



- The aged gut exhibits microbial dysbiosis with relative pathogen enrichment, impaired intestinal barrier integrity, tight junction disruption, and mucus layer degradation;

- Enhanced paracellular permeability allows luminal factors—including lipopolysaccharide, microbial metabolites, bacterial extracellular vesicles, trimethylamine oxide, bile acids, uremic toxins, amyloid-β protein, altered short-chain fatty acid levels, and pro-inflammatory cytokines—to enter the systemic circulation.

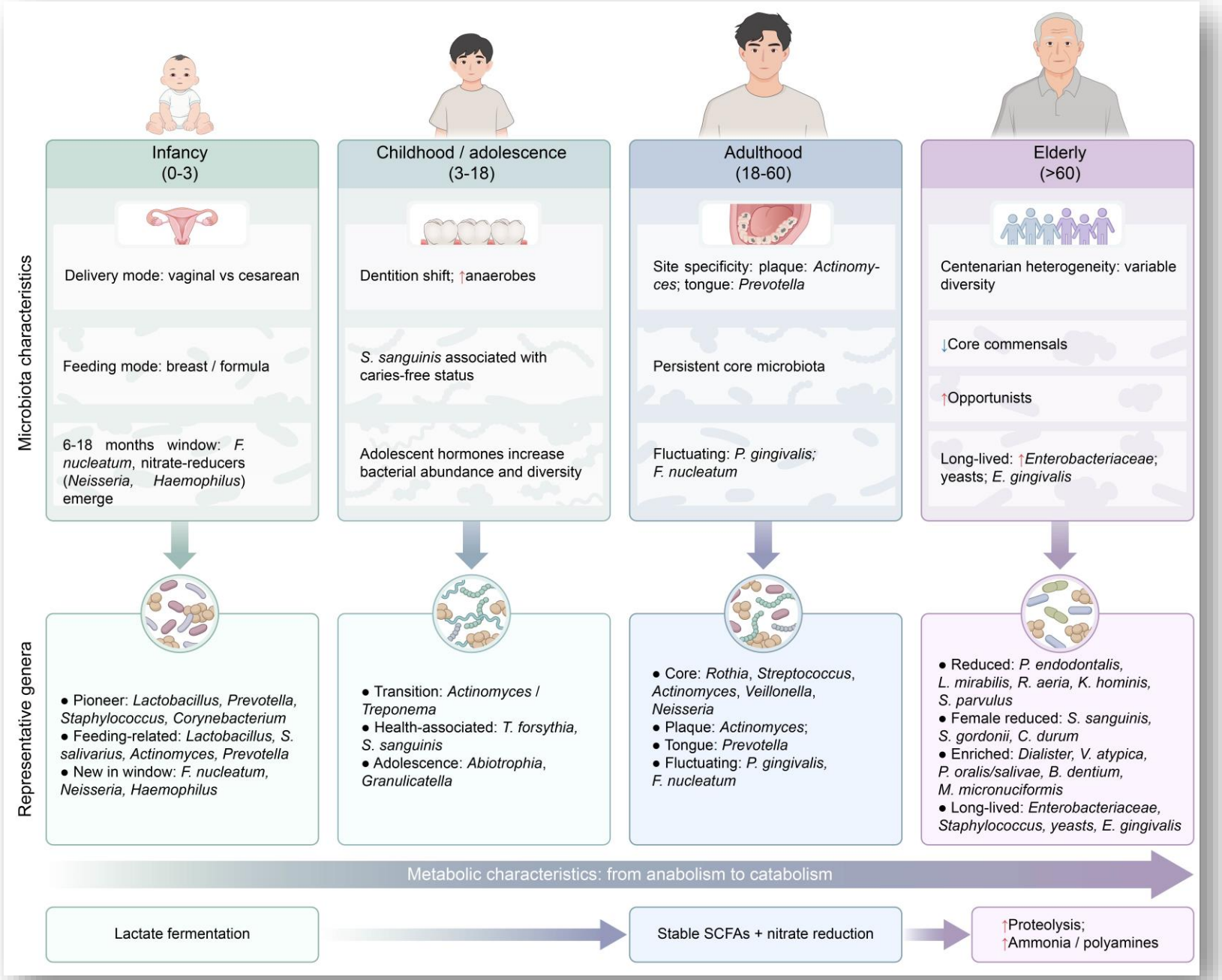
Lifespan dynamics of the gut microbiome and microbiome-targeted anti-aging interventions



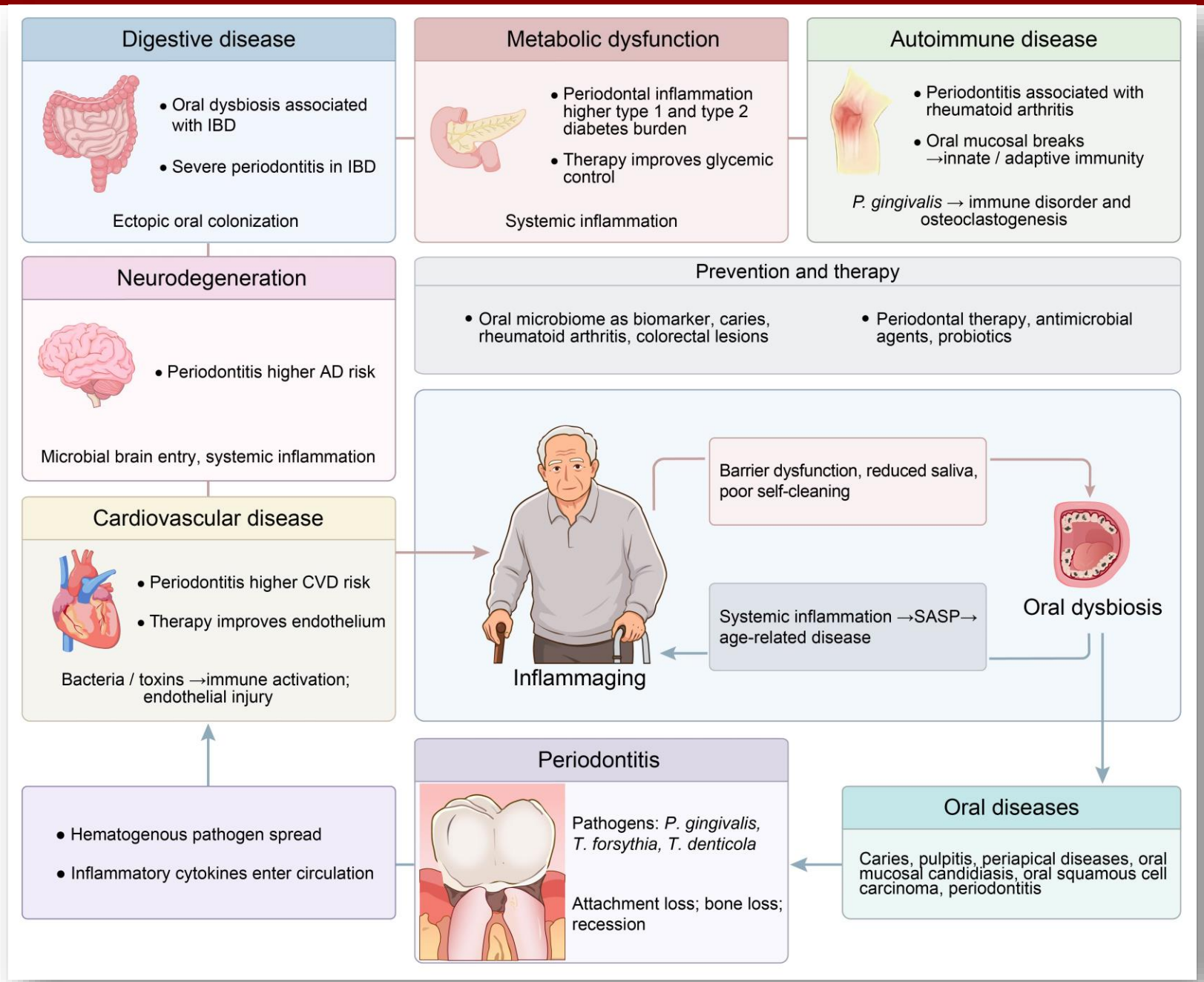
The full lifespan trajectory of the human gut microbiome with a focus on aging-related remodeling

The gut microbiome-targeted anti-aging intervention strategies, including dietary modification (prebiotics, fiber), probiotics/synbiotics, postbiotics, and fecal microbiota transplantation from young donors

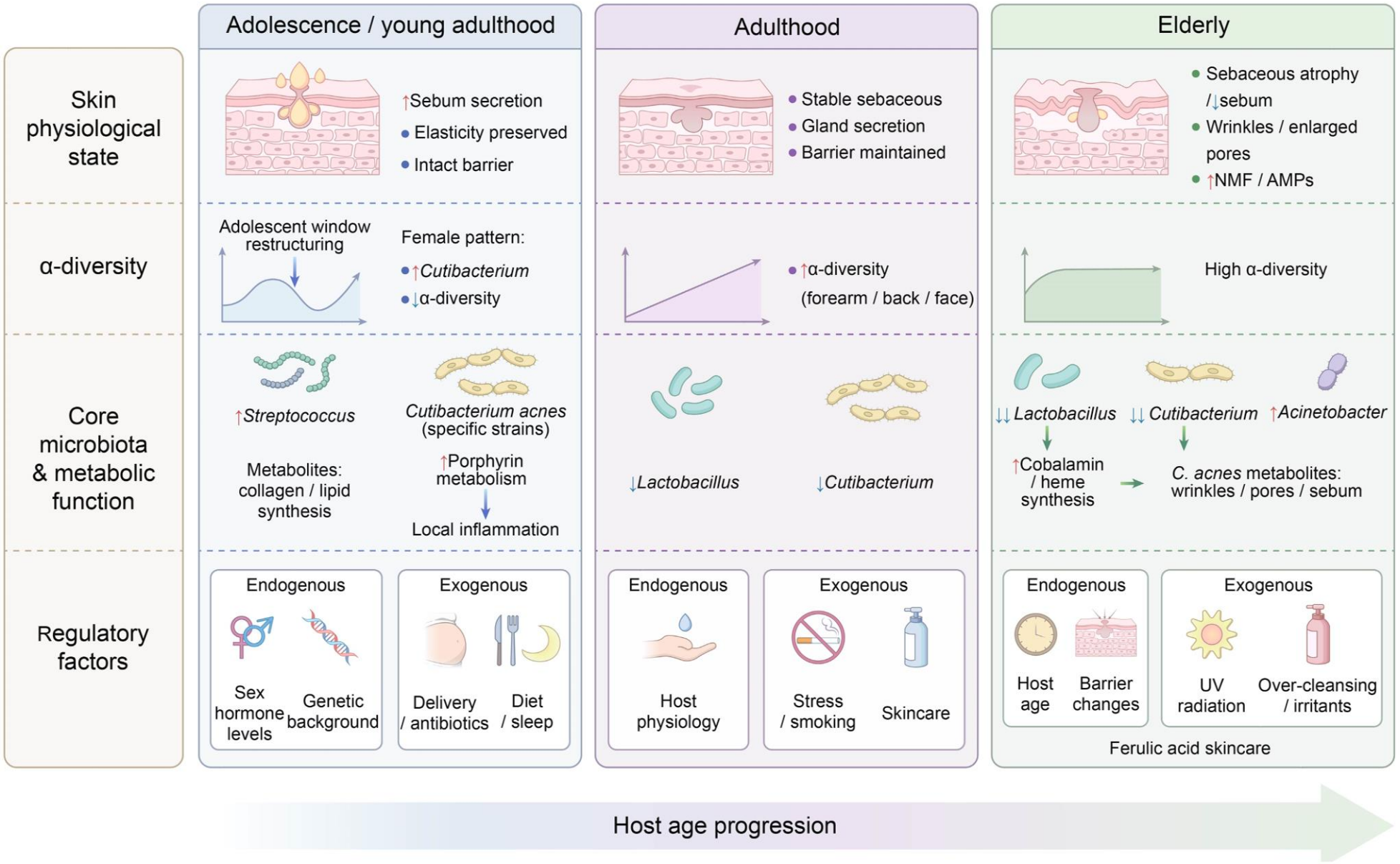
Lifespan succession of the oral microbiome



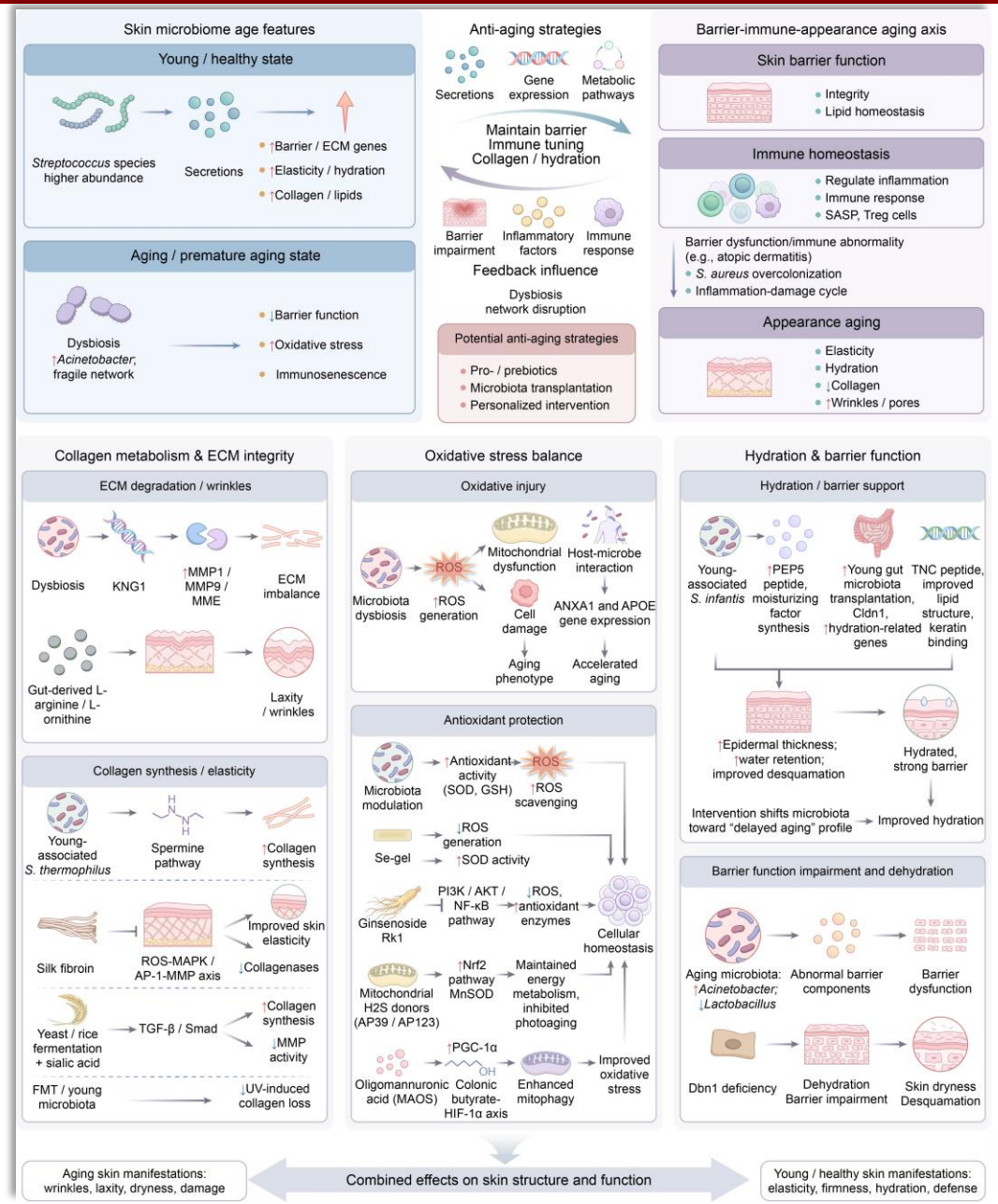
Oral microbiome aging links local craniofacial homeostasis to systemic health



Mechanistic landscape of skin microbiome age dynamics across the host lifespan.



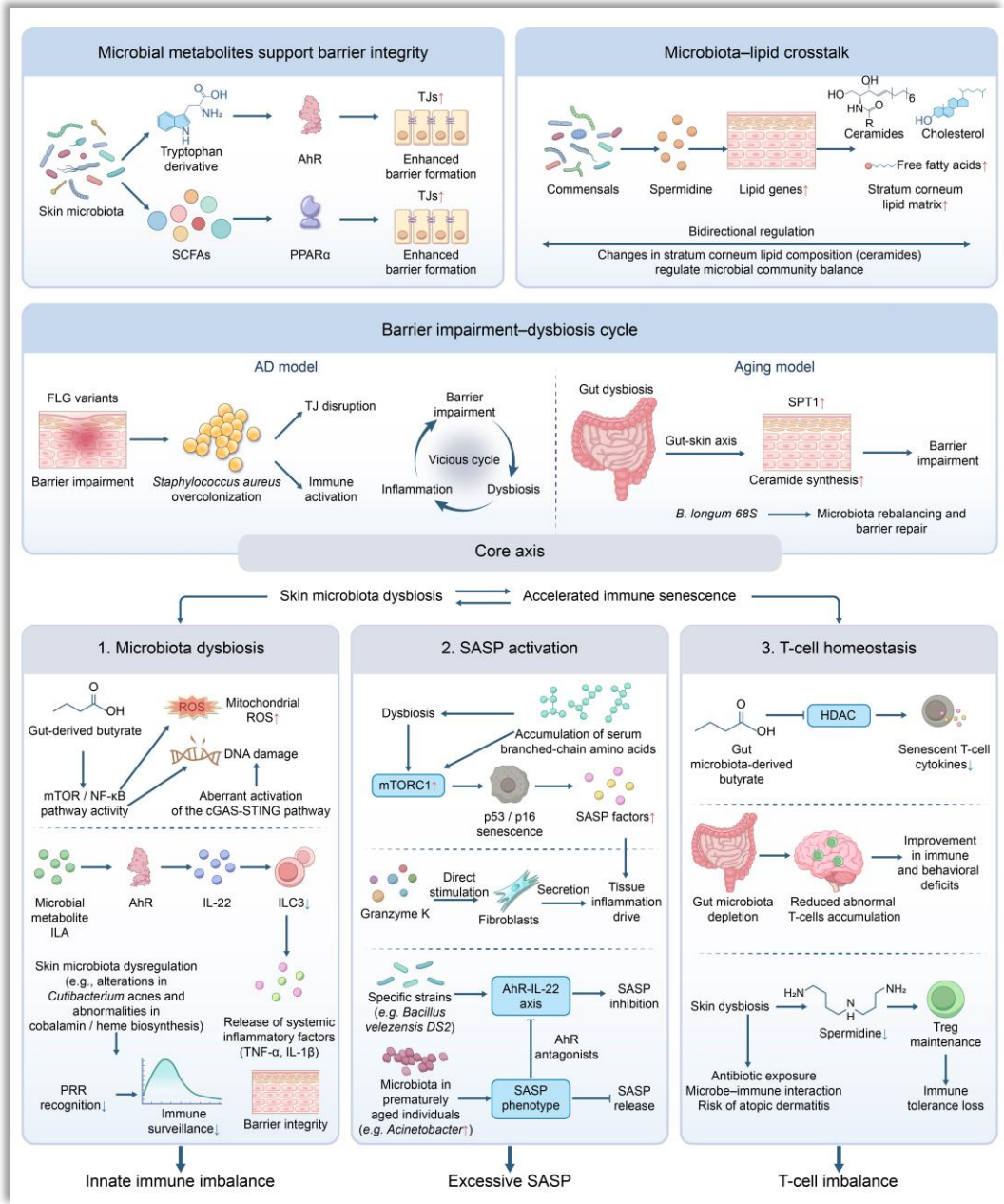
Bidirectional regulation between skin-MA and the barrier-immune-appearance aging axis



- In young, healthy skin with high abundance of specific Streptococcus, microbial metabolites maintain skin barrier integrity, immune homeostasis, and a youthful appearance by modulating the expression of genes governing skin structure and barrier function, thereby promoting collagen and lipid synthesis.

- In aged or prematurely aged skin, impaired barrier function, oxidative stress, and immunosenescence drive skin-MA dysbiosis, which in turn exacerbates barrier damage and inflammatory responses to establish a pathogenic vicious cycle.

Skin microbiome metabolites regulate barrier homeostasis and contribute to immune senescence



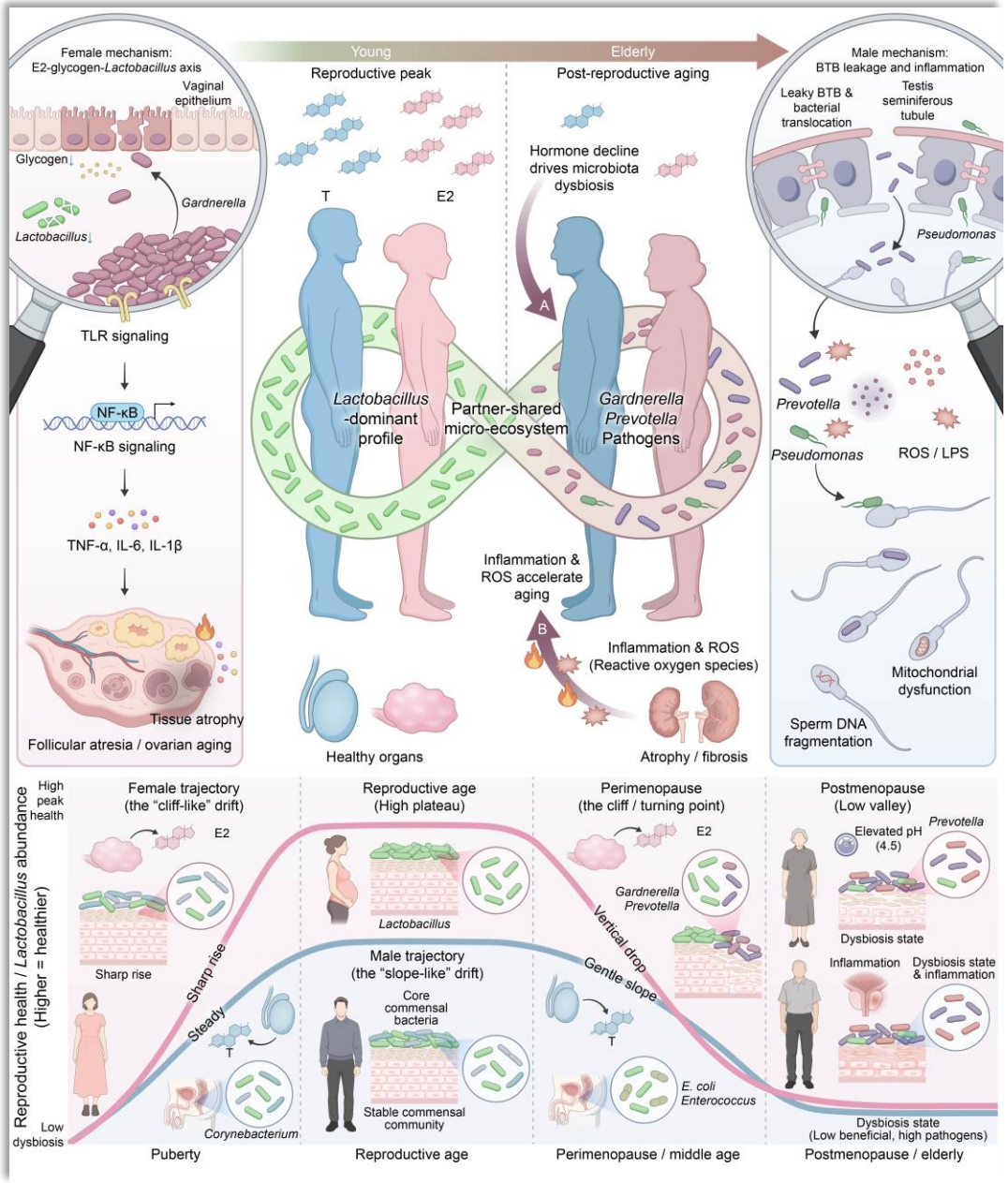
- Microbial metabolites activate aryl hydrocarbon receptor and PPARα to upregulate tight junction proteins;
- In aging, gut dysbiosis and reduced SPT1 cause ceramide deficiency; Bifidobacterium longum 6BS intervention restores homeostasis and barrier function.
- Mechanistic network links skin dysbiosis to immune senescence via three pathways:

  (1) metabolic reprogramming;

  (2) SASP induction;

  (3) T cell modulation.

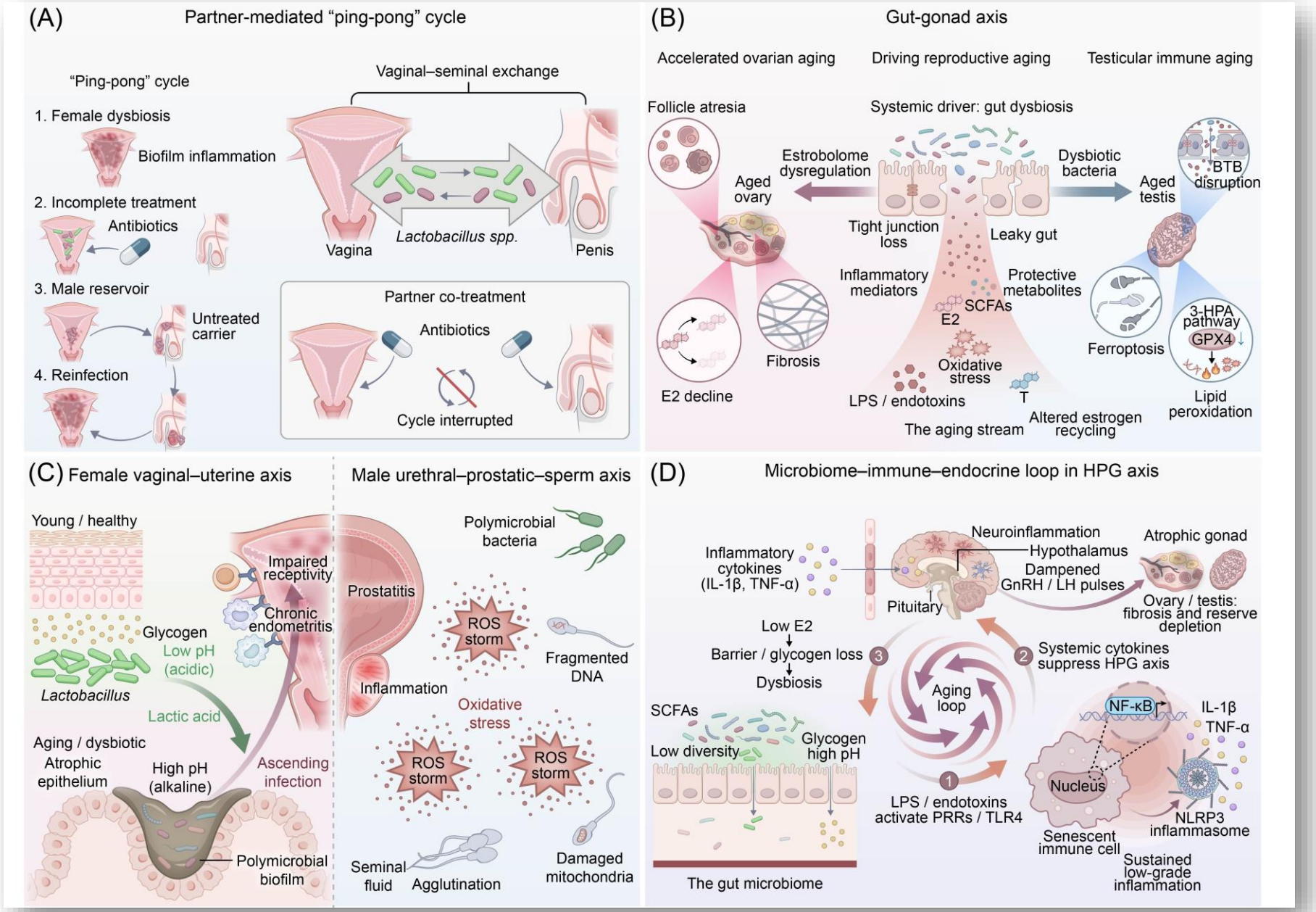
Age-dependent evolution and partner-shared microecosystem aging mechanisms



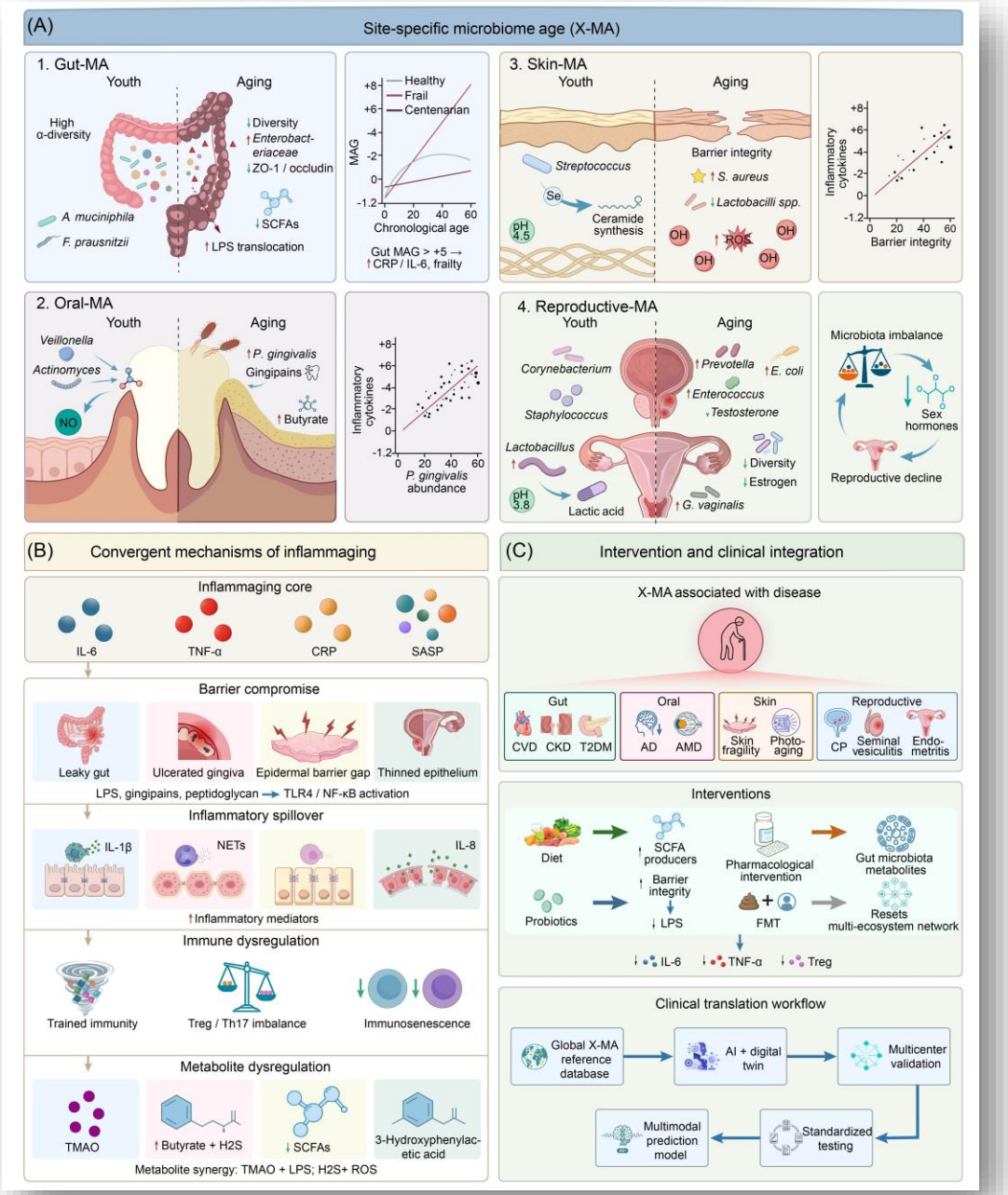
- In females, estrogen depletion triggers an "estrogen-glycogen-inflammation" cycle that activates TLR/NF-κB signaling to accelerate ovarian senescence;
- In males, Testosterone disrupts the blood-testis barrier, with LPS inducing ROS to impair spermatogenesis;

- Female microbiota exhibits a puberty-related steep rise, reproductive-age Lactobacillus-dominated plateau, and perimenopausal cliff-like decline into persistent post-menopausal dysbiosis.;
- Male microbiota shows a gradual puberty-related rise, reproductive-age stability, and middle-age slow drift toward pro-inflammatory dysbiosis with E. coli and Enterococcus enrichment

Integrated host-microbiome mechanisms underlying reproductive aging

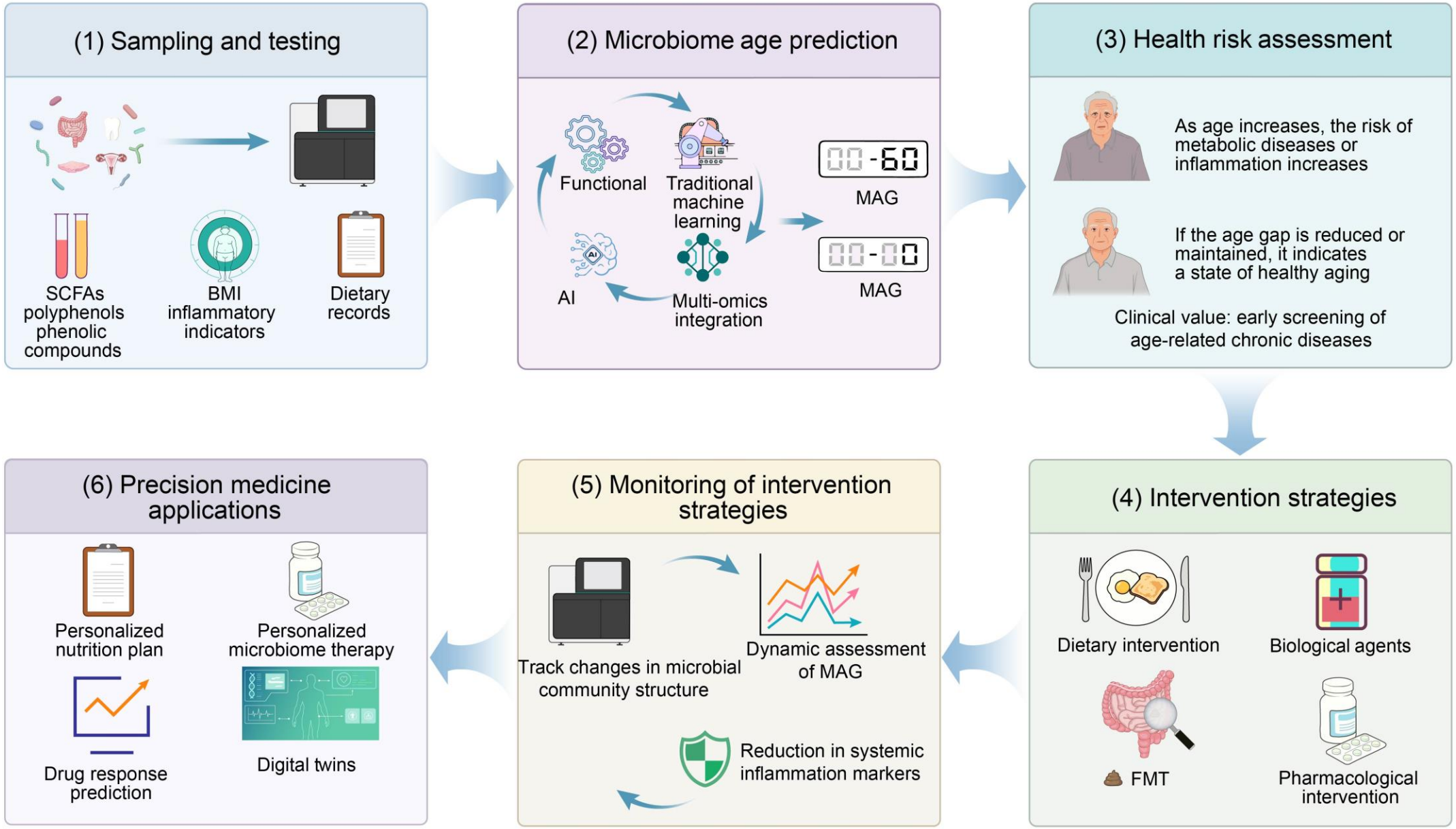


X-MA as a multidimensional readout of inflammagin



- A positive MAG (MAG < 0) signifies younger biological age, while a negative MAG (MAG > 0) indicates accelerated aging and elevated health risks.
- Four convergent pathways to inflammaging-barrier destruction, local inflammation spillover, immune dysregulation, and metabolite dysregulation-collectively driving chronic elevation of IL-6, TNF-α, CRP, and SASP

Translational applications and future implementation of microbiome age



Summary

- ☑Microbiome age is established as a computational biosignature unifying multi-organ aging trajectories;
- ☑Convergent aging trajectories are identified across gut, oral, skin, and reproductive microbiomes;
- ☑Directional microbiome shifts mirror systemic declines in immunity, metabolism, and barrier function;
- ☑Microbiome age serves as a dual biomarker predicting systemic risks and local vulnerabilities, enabling precision health assessment.

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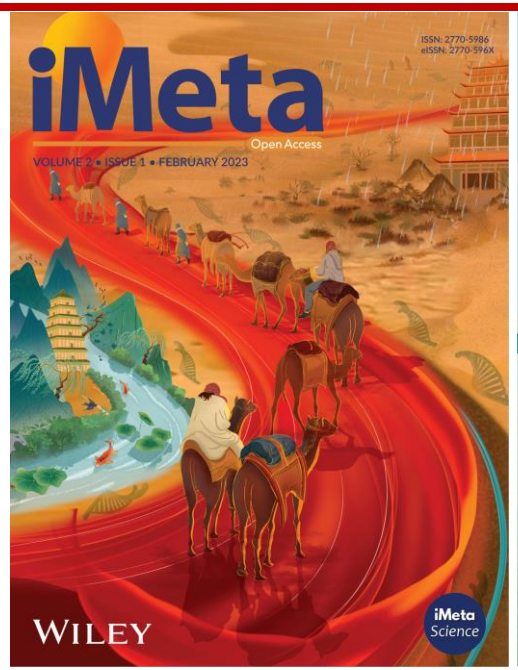

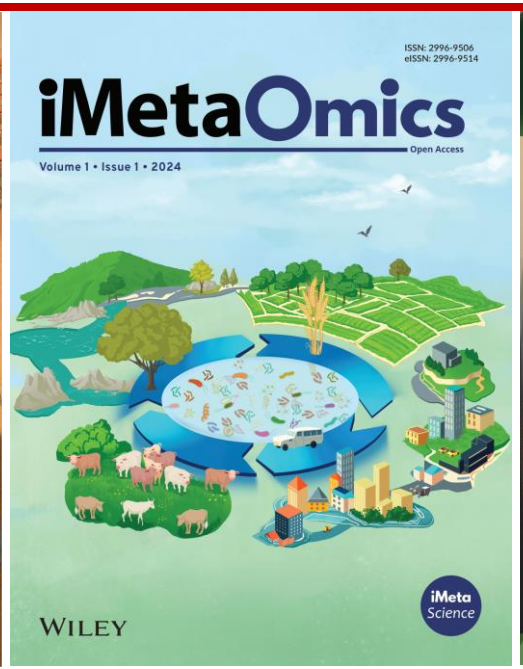

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