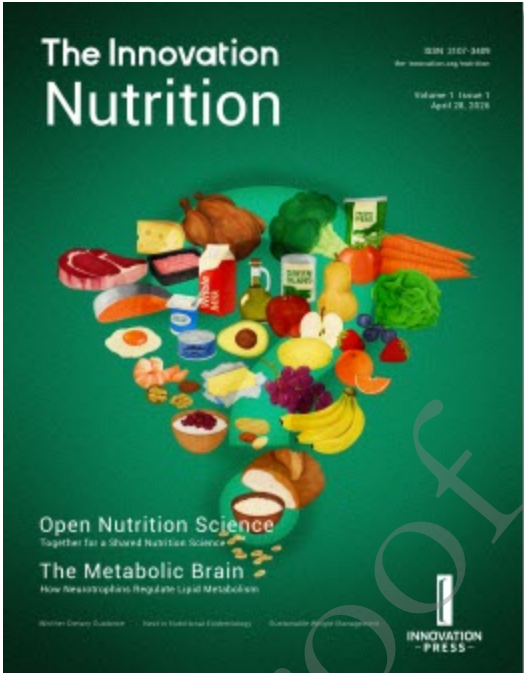




Beyond glucose: How early lifestyle intervention rewires the long-term trajectory of multimorbidity and healthy aging

Journal:	<i>The Innovation Nutrition</i>
Manuscript ID	TIN-2026-0042.R2
Manuscript Type:	Commentary
Keywords:	Prediabetes, Lifestyle intervention, Multimorbidity, Healthy aging, Metformin



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Beyond glucose: How early lifestyle intervention rewires the long-term trajectory of multimorbidity and healthy aging

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Intensive lifestyle intervention and metformin are established strategies for preventing type 2 diabetes, yet their comparative effects on long-term multimorbidity remain uncertain. This commentary synthesizes evidence from landmark prevention trials and

the recent 21-year follow-up of the US Diabetes Prevention Program to evaluate how early interventions shape chronic disease accumulation. Intensive lifestyle modification consistently reduces long-term multimorbidity risk, whereas metformin shows no significant benefit compared with placebo despite similar efficacy in delaying diabetes. Mechanistically, lifestyle acts as a form of systemic biological reprogramming, simultaneously modulating inflammation, mitochondrial function, and gut microbiome composition to create a broad shield against multisystem aging. In contrast, metformin primarily targets hepatic glucose metabolism, pathways insufficient to counteract the diverse hallmarks driving multimorbidity. Current evidence is limited by homogeneous populations, self-reported behavioral data, and incomplete characterization of molecular mediators linking early lifestyle changes to decades-later outcomes. Future priorities include integrated trials that combine lifestyle with next-generation metabolic therapies, such as GLP-1 receptor agonists; multi-omics profiling to elucidate mechanisms; and broader inclusion of diverse demographic groups. For individuals with prediabetes, current data support prolonged lifestyle intervention as the foundational strategy for preserving healthspan rather than merely preventing hyperglycemia. Clinicians should prioritize sustained behavioral programmes and explore synergistic combinations with emerging pharmacotherapies to optimize healthy aging

INTRODUCTION

Multimorbidity has superseded single-disease pathology as the defining challenge of aging societies, contributing substantially to disability, mortality, and escalating healthcare costs worldwide. Three landmark trials—the Da Qing Diabetes Prevention Study, the Finnish Diabetes Prevention Study (DPS), and the US Diabetes Prevention Program (DPP)—established intensive lifestyle intervention as the cornerstone of type 2 diabetes prevention. However, whether preventing diabetes translates to healthier aging and reduced multimorbidity remains uncertain. In this issue of *JAMA*, *Salive et al.* report that intensive lifestyle intervention, but not metformin, significantly lowers the long-term risk of multimorbidity among adults with prediabetes, using the DPP follow-up data.¹ In that study, multimorbidity was defined as the presence of two or more of 15 common chronic conditions. Beyond summarizing these findings, this commentary interprets the DPP follow-up results in the broader context of the Da Qing and Finnish DPS trials and argues for a shift from glucose-centered diabetes prevention toward healthspan-centered prevention, while recognizing multimorbidity as a more meaningful endpoint for evaluating long-term preventive interventions. This perspective highlights lifestyle intervention not merely as a strategy for delaying diabetes, but as a systems-level intervention that may rewire the long-term trajectory of multimorbidity and healthy aging across the life course (**Figure 1**).

INTERVENTION DURATION AND THE LEGACY EFFECT

The divergence in long-term outcomes among landmark trials offers critical mechanistic insights. While all three studies reduced diabetes incidence, only the *Da*

Qing study demonstrated significant reductions in cardiovascular and all-cause mortality after 30 years of follow-up,² whereas comparable survival benefits were absent in the DPS and DPP. This discrepancy likely stems from intervention duration. The *Da Qing* study maintained structured lifestyle support for six years, nearly double the duration of the Finnish and US trials. Importantly, the long-term benefits of lifestyle intervention likely result from the combined effects of sustained dietary improvement, regular physical activity, weight loss, long-term adherence, and sufficient intervention duration. Collectively, these interconnected components may alter the rate of chronic disease accumulation by embedding durable changes in metabolic regulation, vascular health, and inflammatory tone. Thus, multimorbidity reflects a dynamic process modifiable by behavioral patterns established decades earlier.

WHEN DIABETES PREVENTION IS NOT ENOUGH

The most provocative finding from *Salive et al.* is the null effect of metformin on multimorbidity. Metformin has long been championed as a potential geroprotective agent with purported benefits for aging, cancer, cardiovascular disease, and longevity.³ The prospect that this widely available and inexpensive pill could delay biological aging has sparked both scientific enthusiasm and public expectations. However, despite delaying diabetes onset similarly to lifestyle intervention, metformin did not reduce long-term multimorbidity risk compared to placebo.¹ This challenges the assumption that glycemic control or diabetes delay inevitably confers broader healthy aging benefits. The distinction lies between disease-specific prevention and systemic protection. A therapy targeting a single metabolic pathway may successfully mitigate diabetes risk without

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89 influencing the diverse biological processes driving multisystem chronic disease
90 accumulation.

91
92 **WHY MULTIMORBIDITY REQUIRES MORE THAN GLUCOSE CONTROL**

93 In the DPP follow-up study, multimorbidity was defined as the presence of two or
94 more of 15 common chronic conditions, reflecting the accumulation of chronic diseases
95 across multiple organ systems. Multimorbidity is therefore fundamentally a multisystem
96 outcome driven by interconnected hallmarks of aging, including chronic inflammation,
97 mitochondrial dysfunction, immune dysregulation, and loss of physiological resilience.
98 These biological processes contribute to the development of diverse chronic conditions
99 rather than diabetes alone.⁴ Metformin, despite its reputation as a potential geroprotector,
100 functions primarily as a targeted metabolic modulator. Its actions, e.g., suppressing
101 hepatic gluconeogenesis, activating AMP-activated protein kinase (AMPK), and
102 improving insulin sensitivity, are centred on glucose homeostasis. While metformin
103 exhibits pleiotropic properties, including modest anti-inflammatory and microbiome-
104 modulating effects, these are insufficient to counteract the broad, multisystem biological
105 deterioration that characterizes multimorbidity.³ Consequently, the data from *Salive et al.*
106 suggest that simply decelerating the progression to diabetes via a single molecular
107 pathway does not equate to preserving healthspan across diverse organ systems. Effective
108 prevention of multimorbidity requires therapeutic strategies that address the systemic
109 biological roots of aging rather than isolated metabolic surrogates.

LIFESTYLE INTERVENTION AS SYSTEMIC BIOLOGICAL REPROGRAMMING

Although the DPP follow-up study demonstrated that lifestyle intervention was associated with a sustained reduction in multimorbidity, the biological mechanisms underlying this long-term benefit remain incompletely understood. If multimorbidity reflects the cumulative consequences of multisystem aging, the superiority of lifestyle intervention may stem from its capacity to function as a form of systemic biological reprogramming. In contrast to pharmacotherapy, which typically targets a specific receptor or enzyme, lifestyle intervention integrates multiple complementary components, including sustained dietary modification, regular physical activity, weight management, and long-term behavioral adherence, thereby exerting coordinated, pleiotropic effects across multiple physiological networks⁴.

At the cellular level, lifestyle interventions may influence several hallmarks of aging. Regular physical activity has been associated with enhanced mitochondrial biogenesis, improved metabolic flexibility, and maintenance of proteostasis. Concurrently, dietary optimization may reduce inflammatory burden and oxidative stress while modulating nutrient-sensing pathways (such as mTOR and sirtuins) that regulate longevity. Furthermore, emerging evidence also suggests that lifestyle-induced changes in the gut microbiome may contribute to increased short-chain fatty acid production, improved intestinal barrier integrity, and more balanced systemic immune responses.

Collectively, these interconnected adaptations may help explain why lifestyle intervention may confer broader physiological resilience across cardiovascular, renal, metabolic, and neurological systems simultaneously. This systems-level perspective may

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also help explain why the *Da Qing* study observed a legacy effect on mortality and multimorbidity that pharmacological glucocentricity therapy failed to replicate. Rather than merely controlling a metabolic risk factor, lifestyle intervention may modify the biological trajectory of aging through coordinated effects across multiple physiological systems.

TOWARD INTEGRATED STRATEGIES FOR HEALTHY AGING

While *Salive et al.* provide compelling evidence for the long-term superiority of lifestyle, key questions remain. The generalizability of these findings to younger, metabolically healthy, or established disease populations is unknown. In addition, the precise molecular pathways linking early lifestyle intervention to reduced multimorbidity two decades later warrant elucidation through multi-omics and analyses of biological aging biomarkers.

More broadly, these findings necessitate a paradigm shift from disease-centered to multimorbidity-centered prevention. Future trials should prioritize composite endpoints reflecting chronic disease accumulation rather than single-disease outcomes. Importantly, this does not advocate replacing pharmacotherapy with lifestyle intervention. Rather, it underscores the need for integrated models combining behavioral and pharmacological approaches. In this context, diabetes prevention has also evolved beyond a glucose-centered paradigm. The emergence of glucagon-like peptide-1 receptor agonists (GLP-1RAs),⁵ together with dual incretin agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and α -glucosidase inhibitors, reflects the ongoing transition from glucose-centered management toward broader cardiometabolic protection. These therapies may

157 complement, rather than compete with, lifestyle intervention, providing a more
158 comprehensive strategy for multimorbidity prevention and healthy aging.

159 As illustrated in **Figure 1**, the future of preventive medicine lies not in choosing
160 between lifestyle intervention and pharmacotherapy, but in optimizing their integration to
161 slow biological aging, reduce multimorbidity, and extend healthy life expectancy. The
162 ultimate goal transcends diabetes prevention; it is the preservation of functional health,
163 resilience, and healthspan throughout the aging process.

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FIGURE LEGEND

Figure 1. Proposed framework illustrating how early lifestyle intervention extends beyond glucose control to reshape the long-term trajectory of multimorbidity and healthy aging, compared with metformin.

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AUTHOR CONTRIBUTIONS

LC: conceptualization, methodology, supervision, and writing—original draft preparation. GL: visualization, literature review, and writing—reviewing and editing. DD, ML, and CZ: critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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Interventions



Prediabetes



Healthy diet



Regular physical activity



Weight reduction

The Innovation Nutrition



Metformin therapy



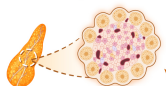
Biological pathways

Shared and divergent mechanisms

Shared metabolic effects



Improved glycemic control



Reduced insulin resistance



Delayed onset of type 2 diabetes

Lifestyle-dominant pathways



Reduced adiposity



Improved mitochondrial function



Reduced inflammation



Improved endothelial function



Gut microbiome modulation



Preserved physical resilience

Metformin-dominant pathways



Reduced hepatic glucose production



Altered cellular energetics



Limited downstream effect on multimorbidity



AMPK activation



Gut-mediated metabolic effects

Long-term outcomes

Diabetes prevention



&



Both lifestyle intervention and metformin can delay or prevent type 2 diabetes

<https://mc03.manuscriptcentral.com/innovation-nutrition>

Multimorbidity and healthy aging



Lifestyle intervention is associated with lower long-term multimorbidity



Metformin is not significantly associated with lower multimorbidity