Multidomain Lifestyle Interventions for Dementia Prevention: From Mechanisms to Clinical Implementation.

Abstract

Background: Dementia represents one of the most pressing global health challenges of the 21st century, with over 55 million people currently affected and projections exceeding 150 million by 2050. Given the multifactorial etiology of late-onset dementia, interventions targeting multiple modifiable risk factors simultaneously have emerged as the most promising prevention strategy. The 2024 Lancet Commission on dementia identified 14 modifiable risk factors accounting for approximately 45% of global dementia cases, providing a strong rationale for multidomain approaches.

Methods: We conducted a narrative review of the literature by searching PubMed, Web of Science, and Google Scholar databases using combinations of the following terms: "multidomain intervention," "dementia prevention," "lifestyle intervention," "cognitive decline," "FINGER trial," "modifiable risk factors," and "neuroplasticity." We included randomized controlled trials, systematic reviews, meta-analyses, and observational studies published primarily between 2014 and 2025. Landmark trials and their subgroup analyses, biological mechanism studies, and global adaptation initiatives were prioritized. Reference lists of key articles were additionally hand-searched for relevant publications.

Results: The FINGER trial (n = 1,260) demonstrated that a two-year multidomain intervention combining diet, exercise, cognitive training, social activity, and vascular risk management produced 25% greater improvement in overall cognitive performance compared to controls, with 83% greater improvement in executive function and 150% in processing speed. The MAPT trial (n = 1,680) showed cognitive benefits predominantly in higher-risk subgroups, including those with positive amyloid biomarkers. The preDIVA trial (n = 3,526) yielded neutral primary results but suggested benefits in participants with untreated hypertension. The World-Wide FINGERS network has expanded to over 60 countries. Biological mechanisms include enhanced BDNF-mediated neuroplasticity, neuroinflammatory modulation, improved cerebrovascular function via VEGF signaling, dietary neuroprotection through anti-oxidant and anti-inflammatory pathways (Mediterranean

diet: 11–30% risk reduction for cognitive disorders), and epigenetic modifications promoting neuroprotective gene expression.

Conclusion: Multidomain lifestyle interventions represent the most evidence-based non-pharmacological strategy currently available for dementia prevention. Risk stratification, precision prevention using blood-based biomarkers, digital health delivery, and combined lifestyle-pharmacological approaches (e.g., MET-FINGER) are emerging as key future directions. Significant challenges remain regarding optimal intervention protocols, long-term adherence, equitable access in diverse populations, and scalable clinical implementation. Integration of multidomain prevention strategies into clinical guidelines and public health policy is warranted.

Keywords: dementia prevention; multidomain intervention; FINGER trial; modifiable risk factors; lifestyle medicine; cognitive decline; neuroplasticity

1. Introduction

Dementia is a progressive neurodegenerative syndrome characterized by deterioration in cognitive function, behavioral disturbances, and loss of functional independence. Alzheimer's disease is the most prevalent form, accounting for approximately 60–70% of all cases. According to the World Health Organization, over 55 million people worldwide currently live with dementia, and this figure is expected to rise dramatically as populations age. The global economic burden of dementia was estimated at over 1.3 trillion US dollars in 2019 and is projected to surpass 2.8 trillion by 2030.

Historically, dementia research focused predominantly on pharmacological interventions targeting disease-specific pathology, particularly amyloid-beta and tau accumulation in Alzheimer's disease. However, decades of clinical trial failures underscored the limitations of single-target therapeutic approaches. Meanwhile, converging epidemiological evidence revealed that a substantial proportion of dementia cases may be attributable to modifiable risk factors operating across the lifespan.

The Lancet Commission on dementia prevention, intervention, and care has been instrumental in quantifying this preventive potential. The 2020 report by Livingston et al. identified 12 modifiable risk factors—including low education, hearing loss, hypertension, smoking, obesity, depression, physical inactivity, diabetes, excessive alcohol consumption,

traumatic brain injury, air pollution, and social isolation—that collectively account for approximately 40% of dementia cases worldwide. The 2024 update of the Lancet Commission, published in The Lancet by Livingston, Huntley, Liu et al., added untreated vision loss and high LDL cholesterol to the list, increasing the estimated proportion of potentially preventable cases to approximately 45%.

Given the complex, multifactorial etiology of late-onset dementia, interventions targeting several risk factors and mechanisms simultaneously are likely necessary for optimal preventive effects. This rationale has driven the development and testing of multidomain lifestyle interventions, which represent the most promising non-pharmacological strategy for dementia prevention currently available. This narrative review aims to synthesize the current evidence base on multidomain lifestyle interventions for dementia prevention, examining the mechanistic underpinnings, key clinical trial evidence, global adaptation efforts, and the challenges that remain in translating research into widespread clinical implementation.

2. Modifiable Risk Factors and the Rationale for Multidomain Approaches

The recognition that dementia risk is modulated by lifestyle and environmental factors across the life course has fundamentally transformed the field. Risk factors operate through multiple, often overlapping pathways—vascular, inflammatory, metabolic, and psychosocial—that collectively accelerate neurodegeneration and impair cognitive reserve.

2.1 Life-Course Risk Factor Framework

The Lancet Commission framework stratifies modifiable risk factors by life stage. In early life (before age 18), less education is the primary modifiable factor, as it limits the development of cognitive reserve. During midlife (ages 18–65), hearing loss, traumatic brain injury, hypertension, excessive alcohol consumption, and obesity emerge as key contributors. In later life (over age 65), smoking, depression, social isolation, physical inactivity, diabetes, air pollution, untreated vision loss, and elevated LDL cholesterol become particularly relevant. This life-course approach underscores that dementia prevention is not limited to late-life interventions but requires sustained engagement across decades.

2.2 Synergistic and Cumulative Effects

A critical insight from epidemiological research is that risk factors rarely operate in isolation. Hypertension accelerates cerebrovascular damage, which is compounded by diabetes-related metabolic dysfunction and physical inactivity-associated loss of vascular fitness. Depression diminishes social engagement and reduces adherence to healthy lifestyle behaviors, creating reinforcing cycles of risk accumulation. These interactions provide the fundamental rationale for multidomain interventions: addressing a single risk factor in isolation may yield only modest effects, whereas simultaneously targeting multiple factors may produce synergistic benefits that exceed the sum of individual interventions.

2.3 The Concept of Cognitive Reserve

Cognitive reserve, the capacity of the brain to maintain function despite accumulating pathology, is modulated by lifetime intellectual, social, and physical engagement. Education, occupational complexity, bilingualism, and leisure activities all contribute to building cognitive reserve. Multidomain interventions are uniquely positioned to enhance cognitive reserve through multiple simultaneous channels, combining cognitive stimulation with physical activity, dietary optimization, and social engagement to reinforce both brain structure and functional resilience.

3. Biological Mechanisms Underlying Multidomain Interventions

3.1 Neurotrophic Signaling and Neuroplasticity

Physical exercise is one of the most potent non-pharmacological stimulators of brain-derived neurotrophic factor (BDNF), a key mediator of synaptic plasticity, neurogenesis, and neuronal survival. Aerobic exercise increases BDNF expression in the hippocampus, the brain region most critical for memory formation and among the earliest affected in Alzheimer's disease. A meta-analysis of 36 randomized controlled trials in Alzheimer's disease animal models demonstrated that exercise significantly elevates BDNF levels in both hippocampal and cortical regions, with swimming producing the largest effect sizes followed by treadmill exercise and voluntary wheel running (standardized mean difference = 0.98, $P < 0.00001$).

Resistance exercise contributes additional neuroplasticity benefits through distinct myokine-mediated pathways. Progressive resistance training increases circulating insulin-like growth factor-1 (IGF-1) and promotes the release of exercise-induced myokines such as irisin and cathepsin B, which cross the blood-brain barrier and stimulate hippocampal neurogenesis.

Romero Garavito and colleagues (2024) reviewed these pathways in Frontiers in Neurology, highlighting that moderate-intensity aerobic exercise performed for 30–40 minutes, 3–4 times per week optimally stimulates BDNF production and hippocampal neurogenesis.

3.2 Neuroinflammatory Modulation

Chronic low-grade neuroinflammation, characterized by sustained microglial activation and elevated pro-inflammatory cytokines including interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, is a recognized contributor to neurodegenerative processes. Multidomain lifestyle interventions modulate neuroinflammation through several complementary pathways. Regular physical exercise shifts microglial phenotype from the pro-inflammatory M1 state toward the anti-inflammatory M2 phenotype, reducing reactive astrogliosis and supporting oligodendrocyte precursor cell differentiation. Dietary patterns rich in polyphenols, omega-3 fatty acids, and antioxidants—such as the Mediterranean diet—suppress nuclear factor-kappa B signaling and enhance endogenous antioxidant defense systems. Social engagement and cognitive stimulation reduce chronic stress-related cortisol elevation, which when sustained contributes to hippocampal atrophy and inflammatory cascades.

3.3 Cerebrovascular Mechanisms

Vascular dysfunction is increasingly recognized as a major driver of cognitive decline, contributing to both vascular dementia and mixed dementia pathology. Hypertension, diabetes, obesity, and dyslipidemia damage the cerebral microvasculature, leading to white matter hyperintensities, lacunar infarcts, and impaired cerebral blood flow. Multidomain interventions that include vascular risk factor management—through blood pressure optimization, glycemic control, lipid management, and lifestyle modification—can attenuate these processes. The FINGER trial demonstrated improved cerebral blood flow as one mechanism underlying cognitive benefits. Exercise independently enhances endothelial function, promotes angiogenesis through vascular endothelial growth factor (VEGF) signaling, and improves neurovascular coupling.

3.4 Dietary Neuroprotection

The Mediterranean diet, characterized by high consumption of fruits, vegetables, whole grains, legumes, nuts, olive oil, and fish, with moderate intake of dairy and limited red meat, has been associated with substantial reductions in dementia risk. A recent comprehensive

meta-analysis published in GeroScience analyzed data from studies published between 2000 and 2024 and reported that adherence to the Mediterranean diet was associated with an 11–30% reduction in the risk of cognitive impairment, dementia, and Alzheimer's disease (hazard ratios: 0.82 for cognitive impairment, 0.89 for dementia, and 0.70 for Alzheimer's disease). The neuroprotective mechanisms include antioxidant activity from polyphenols and carotenoids, anti-inflammatory effects of omega-3 polyunsaturated fatty acids, and inhibition of amyloid-beta deposition by vitamin E, folate, and flavonoids.

The MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay), developed by Morris and colleagues at Rush University, is a hybrid dietary pattern that specifically targets foods with putative neuroprotective properties. In the observational Memory and Aging Project study, high adherence to the MIND diet was associated with cognitive decline equivalent to being 7.5 years younger. However, a three-year randomized controlled trial (Barnes et al., New England Journal of Medicine, 2023) found that the MIND diet produced cognitive improvements similar to those of a control diet with mild caloric restriction, suggesting that dietary improvement per se—regardless of the specific pattern—may confer benefit.

3.5 Epigenetic Modifications

Emerging evidence suggests that lifestyle interventions can induce epigenetic changes that promote neuroprotection. Exercise modifies DNA methylation patterns in genes related to neuroplasticity and inflammation, upregulates histone acetylation at BDNF gene promoters, and modulates microRNA expression profiles involved in synaptic plasticity. Dietary polyphenols, particularly resveratrol and curcumin, activate sirtuin-mediated deacetylation pathways and modulate histone modifications associated with neuroprotective gene expression. These epigenetic mechanisms may explain the sustained benefits of lifestyle interventions observed even after active intervention periods cease.

4. Landmark Clinical Trials

4.1 The FINGER Trial

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was the first large-scale randomized controlled trial to demonstrate that a multidomain lifestyle intervention can significantly improve cognitive function in at-risk older adults. Led by Professor Miia Kivipelto, the trial enrolled 1,260 Finnish adults aged 60–

77 years who were at increased risk for dementia based on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score. Participants were randomized 1:1 to a two-year multidomain intervention or regular health advice.

The intervention comprised five simultaneous components: (1) nutritional counseling based on Finnish and Nordic Nutrition Recommendations; (2) physical exercise including progressive aerobic, strength, and balance training; (3) computerized cognitive training targeting memory, executive function, and processing speed; (4) social stimulation through group-based activities; and (5) intensive monitoring and management of cardiovascular and metabolic risk factors including blood pressure, cholesterol, blood glucose, and body weight.

Results published by Ngandu, Lehtisalo, Solomon et al. (2015) in The Lancet demonstrated that the intervention group showed 25% greater improvement in overall cognitive performance compared to the control group. Domain-specific analyses revealed even more striking benefits: 83% greater improvement in executive function, 150% greater improvement in psychomotor processing speed, and 40% greater improvement in complex memory tasks. The control group had a 30% greater risk of developing cognitive impairment during the two-year follow-up. Subgroup analyses by Solomon et al. (2018) in JAMA Neurology showed that carriers of the apolipoprotein E epsilon-4 (APOE4) allele—the strongest genetic risk factor for late-onset Alzheimer's disease—derived clear cognitive benefits from the intervention.

The FINGER trial also demonstrated broader health benefits beyond cognition. The intervention group reported better health-related quality of life (Strandberg et al., 2017), and the risk of multimorbidity was reduced by 60% compared to the control group (Marengoni et al., 2018). Longer-term follow-up showed reduced cerebrovascular events (Lehtisalo et al., 2022). Rosenberg et al. (2018) in Alzheimer's & Dementia confirmed that the intervention was beneficial regardless of participants' age, sex, education, socioeconomic status, baseline cognitive performance, or cardiovascular risk level, suggesting broad population applicability.

4.2 The MAPT Trial

The Multidomain Alzheimer Preventive Trial (MAPT) was a three-year multicenter randomized controlled trial conducted in France under the leadership of Bruno Vellas at the Gérontopôle of Toulouse University Hospital. The trial enrolled 1,680 community-dwelling adults aged 70 years and older with subjective memory complaints but without dementia.

Participants were randomized to one of four arms: multidomain intervention alone (nutritional counseling, physical exercise, cognitive stimulation, and preventive consultation), omega-3 polyunsaturated fatty acid supplementation alone, combined multidomain intervention plus omega-3, or placebo.

The primary outcome analysis published by Andrieu, Guyonnet, Coley et al. (2017) in The Lancet Neurology did not show a significant overall effect of either the multidomain intervention or omega-3 supplementation on cognitive decline. However, pre-specified subgroup analyses revealed that participants with higher dementia risk—particularly those with positive amyloid PET scans and those with CAIDE risk scores above the median—showed significant cognitive benefits from the multidomain intervention. This finding highlighted that risk stratification may be essential for identifying populations most likely to benefit from preventive interventions.

4.3 The preDIVA Trial

The Prevention of Dementia by Intensive Vascular Care (preDIVA) trial, led by Moll van Charante, Richard et al. in the Netherlands, was a six-year pragmatic, cluster-randomized controlled trial that enrolled 3,526 community-dwelling adults aged 70–78 years. The intervention consisted of nurse-led, multidomain cardiovascular risk factor management delivered through general practices.

The primary outcome, published in The Lancet in 2016, was neutral: the intervention did not significantly reduce all-cause dementia incidence in the overall study population. However, subgroup analyses revealed potentially meaningful effects. Participants with untreated hypertension at baseline who adhered to the intervention showed reduced dementia risk. The investigators noted that in a healthcare system with already high standards of usual care, the incremental benefit of the intervention may have been too small to detect at the population level. This observation has important implications for the design of future trials and highlights the concept of a “floor effect” in high-quality healthcare settings.

4.4 Comparative Synthesis

Taken together, these three landmark European trials provide complementary insights. FINGER demonstrated clear cognitive benefits of a comprehensive multidomain approach in an at-risk population. MAPT suggested that risk stratification is critical and that benefits may be most pronounced in higher-risk subgroups. preDIVA highlighted that context matters: intervention effects depend on baseline risk levels, adherence, and the quality of existing

care. A Cochrane systematic review by Hafdi, Hoevenaar-Blom, and Richard (2021) concluded that multidomain interventions show promise but that heterogeneity in study designs, populations, and intervention components limits definitive conclusions.

5. The World-Wide FINGERS Network and Global Adaptation

Recognizing the need to validate and adapt the FINGER model across diverse populations, Professor Kivipelto launched the World-Wide FINGERS (WW-FINGERS) network in 2017 in collaboration with the Alzheimer's Association. The network has expanded to include research teams from over 60 countries, making it the largest global collaboration for dementia prevention research.

The WW-FINGERS network operates on a shared core methodology: all member trials implement FINGER-type multidomain interventions while adapting specific components to local cultural, dietary, economic, and healthcare contexts. This approach allows both standardization for scientific rigor and flexibility for cultural relevance.

Key trials within the network include: the US POINTER trial (U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk); MIND-CHINA (Multimodal Interventions to Delay Dementia and Disability in Rural China); the Japan Multimodal Intervention Trial for Prevention of Dementia (J-MINT) and the J-MINT PRIME Tamba study; SMARRT (Systematic Multi-Domain Alzheimer's Risk Reduction Trial) in the United States, which pioneered personalized interventions based on individual dementia risk profiles; AU-ARROW in Australia; Maintain Your Brain (MYB) in Australia, which tested an online delivery model; SUPERBRAIN in Korea; and the MIND-ADmini trial in Sweden, Finland, France, and Germany, which tested the FINGER model in people with prodromal Alzheimer's disease.

A recent comprehensive review by Sugimoto et al. (2025) in Geriatrics and Gerontology International analyzed results from completed WW-FINGERS trials and reported that while three trials demonstrated cognitive improvements, others were hampered by the COVID-19 pandemic. Pre-specified subanalyses across multiple trials consistently showed improvements in modifiable risk factors such as physical inactivity and nutritional status.

6. Digital Health Technologies and Precision Prevention

6.1 Digital Delivery of Multidomain Interventions

The scalability challenge of face-to-face multidomain interventions has driven interest in digital delivery modalities. The Maintain Your Brain trial in Australia demonstrated the feasibility of delivering a multidomain lifestyle intervention entirely online. Digital platforms can provide personalized cognitive training, remote physical activity monitoring through wearable devices, telemedicine-based vascular risk management, and app-based dietary tracking. The COVID-19 pandemic accelerated the development and adoption of digital health technologies for dementia prevention, revealing both opportunities and limitations related to digital literacy, engagement sustainability, and equitable access.

6.2 Precision Prevention and Biomarker-Guided Approaches

The evolving field of precision prevention aims to tailor interventions to individual risk profiles using validated risk scores, genetic information, blood-based biomarkers, and digital phenotyping. The CAIDE risk score, originally developed from Finnish population data, has been widely adopted for risk stratification in dementia prevention trials. Advances in blood-based biomarkers—including plasma amyloid-beta 42/40 ratio, phosphorylated tau (p-tau181, p-tau217), neurofilament light chain, and glial fibrillary acidic protein—now enable the identification of presymptomatic Alzheimer's disease pathology, allowing interventions to be initiated earlier and targeted to those most likely to benefit.

The MET-FINGER trial represents a paradigm-advancing initiative that combines the FINGER lifestyle intervention with metformin as a putative disease-modifying pharmacological agent. This trial is the first to test a combined lifestyle-drug approach in the context of dementia prevention, laying the groundwork for future adaptive platform trials that can simultaneously evaluate multiple intervention combinations in biomarker-defined populations.

7. Challenges and Limitations

Despite the accumulating evidence supporting multidomain lifestyle interventions, several significant challenges remain. First, there is heterogeneity in intervention components, intensity, duration, and delivery modalities across trials, making direct comparison difficult. The optimal "dose" and combination of lifestyle components has not been established. Second, long-term adherence remains problematic: maintaining complex behavioral changes over years to decades is inherently challenging, and dropout rates in prevention trials are substantial. Third, selection bias affects most trials, as participants who volunteer for lifestyle

intervention studies tend to be more health-conscious, educated, and motivated than the general population at risk.

Outcome measurement poses additional challenges. Cognitive decline in at-risk but non-demented populations is gradual, and standard neuropsychological tests may lack sensitivity to detect early, subclinical changes. Dementia incidence as a primary outcome requires very large sample sizes and extended follow-up periods. Composite cognitive scores, while more sensitive, are difficult to interpret clinically and vary across studies.

Equity and accessibility represent crucial implementation concerns. Populations with the highest dementia risk burden—including those in low- and middle-income countries, ethnic minorities, and socioeconomically disadvantaged groups—are systematically underrepresented in prevention trials. The 2024 Lancet Commission emphasizes that individuals in lower-income settings have the most to gain from modifiable risk factor interventions, yet face the greatest barriers to accessing such programs.

Finally, the mechanistic understanding remains incomplete. While multiple biological pathways have been implicated, the relative contribution of each pathway, the degree of synergy between intervention components, and the optimal timing of intervention initiation across the life course require further investigation.

8. Future Directions

Several promising directions are emerging. First, the integration of multidomain lifestyle interventions with pharmacological approaches—exemplified by the MET-FINGER trial—may achieve additive or synergistic effects. As disease-modifying therapies for Alzheimer's disease such as lecanemab enter clinical practice, combining these treatments with lifestyle optimization could represent the standard of prevention care.

Second, adaptive platform trial designs could enable efficient simultaneous evaluation of multiple intervention combinations in biomarker-stratified populations, accelerating the identification of optimal prevention strategies. Third, the integration of artificial intelligence and machine learning for personalized risk assessment, intervention optimization, and real-time adherence monitoring could dramatically enhance the precision and scalability of multidomain programs.

Fourth, greater attention to implementation science is needed. Research must address how to translate evidence-based multidomain interventions into routine clinical practice across

diverse healthcare systems, including primary care integration, health workforce training, reimbursement models, and community-based delivery. Fifth, the WW-FINGERS network provides an unprecedented platform for international data harmonization and collaborative analysis, enabling the identification of population-specific intervention effects and the development of culturally adapted prevention programs.

Finally, a life-course approach to dementia prevention—beginning with childhood education, extending through midlife cardiovascular risk management, and continuing with late-life cognitive and social engagement—represents the aspirational framework for comprehensive dementia risk reduction. As the Lancet Commission envisions, dementia prevention should eventually parallel the success achieved in cardiovascular disease prevention through early detection and sustained risk factor modification.

9. Conclusion

Multidomain lifestyle interventions represent the most evidence-based non-pharmacological strategy currently available for dementia prevention. The FINGER trial established proof of concept, and the expanding WW-FINGERS network is validating this approach across diverse global populations. The 2024 Lancet Commission's identification of 14 modifiable risk factors accounting for 45% of dementia cases provides a compelling public health mandate for action. While significant challenges remain in optimizing intervention protocols, ensuring long-term adherence, achieving equitable access, and understanding mechanistic pathways, the convergence of evidence from epidemiological studies, randomized clinical trials, and biological research supports the integration of multidomain lifestyle interventions into clinical guidelines and public health policy. The ultimate goal—treating dementia prevention with the same rigor and urgency as cardiovascular disease prevention—is increasingly within reach.

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