A Vision for the Next Generation of Clinical Trials for Dementia Risk Reduction: Toward Precision-Prevention

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Precision-prevention offers a transformative opportunity to reduce the growing global burden of dementia by aligning interventions with individual biological risk profiles and harnessing prevention potential across the life course. Building on the foundational successes of multidomain randomized trials, alongside advances in cardiometabolic therapeutics and biomarker science, the next phase of dementia risk reduction requires clinical frameworks that are harmonized, biologically informed, and scalable across health systems globally.

The Problem

Dementia risk reduction is a global health imperative; yet, the clinical trial evidence base remains insufficiently positioned to inform large-scale implementation and policy (1). Despite strong observational evidence and pioneering, well-structured multidomain randomized trials, progress has been constrained by biological heterogeneity, variable intervention intensity, and limited harmonization of cognitive and functional endpoints across studies. As a result, effect sizes are often diluted, comparative inference is limited, and translation beyond research settings remains slow.

The importance of dementia risk reduction has been reaffirmed at the global policy level, including by the World Health Assembly (2), yet prevention efforts remain far less coordinated than those in fields such as oncology or cardiometabolic diseases. At the same time, prevention research has reached a critical inflection point. Blood-based biomarkers now enable biological risk and disease staging years before clinical symptoms (3) (4), genetic and metabolic profiling can identify effect modifiers, and digital tools allow objective monitoring of adherence and scalable delivery beyond specialty clinics (5) (6). Together, these advances make it possible to align prevention strategies more closely with individual risk biology while preserving the multidomain foundations that have demonstrated feasibility and safety.

The field must now transition from earlier generations of dementia prevention trials toward a more integrated and harmonized precision-prevention framework, anchored in biological stratification, scalable delivery, and global applicability, including settings where most future dementia cases will occur (7).

The Missed Opportunity

Despite two decades of compelling observational evidence and substantial investment in multidomain prevention trials, dementia risk-reduction research has yet to achieve its full potential. Many trials have demonstrated feasibility, safety, and modest cognitive benefit, yet their collective impact has been limited by the way evidence is generated and synthesized (8) (9). In the absence of biological stratification, multidomain interventions necessarily average effects across individuals with heterogeneous genetic, metabolic, vascular, and pathological profiles, diluting signals in those most likely to benefit while obscuring non-response in others (10). Similarly, without biomarker-informed endpoints, trials must rely on long follow-up periods and coarse cognitive measures, increasing cost and reducing sensitivity to meaningful biological change (3).

Operational fragmentation further compounds this challenge. Differences in outcome measures, intervention dose, adherence definitions, and analytic approaches limit cross-trial comparability and impede cumulative learning. Adherence, whether to behavioral dose, intervention intensity, or sustained engagement across domains, is consistently linked to cognitive outcomes, yet remains variably defined and inconsistently supported across interventions (11) (12) (13). Beyond behavioral heterogeneity, trials also differ substantially in the biological layers they capture, including biomarkers of interest, sampling matrices and frequency, processing pipelines, and depth of participant metadata, further constraining integration across studies. As a result, prevention science has struggled to move from proof-of-concept to decision-grade evidence that can guide policy, health system planning, and global implementation. The missed opportunity is not a lack of innovation, but a lack of integration: without precision, harmonization, and scalability built into trial design, even effective interventions risk remaining confined to isolated studies rather than shaping a coherent, global prevention strategy. Key knowledge gaps and design priorities are summarized in Box 1.

Why Precision Is Now Possible and Necessary

Dementia risk reduction has entered a qualitatively different phase, in which precision is no longer aspirational but operationally feasible. Several converging advances now allow prevention trials to move beyond broad, population-averaged designs toward biologically informed, analytically efficient, and scalable approaches across settings. Together, these developments make clear that the limitations of past prevention trials reflect the tools available at the time, not the ceiling of what prevention can achieve. Precision is now necessary to convert feasibility into impact.

Biomarkers.

Blood-based biomarkers of Alzheimer's disease and related pathology, including phosphorylated tau, amyloid ratios, neurofilament light, and glial markers, now enable biological risk and disease staging years before clinical symptoms emerge (Figure 1) (3). Their integration into prevention trials can shorten timelines, improve participant enrichment, and provide sensitive intermediate outcomes that reflect disease-relevant processes rather than late-stage cognitive decline alone. Recent work further demonstrates that key Alzheimer's disease biomarkers can be reliably detected from minimally invasive dried blood spot samples, substantially lowering barriers to scalable, population-level screening and longitudinal monitoring (14). Without such biomarkers, prevention trials remain long, costly, and statistically blunt; with them, prevention becomes experimentally tractable.

Genetic and metabolic profiling.

Genetic risk factors such as *APOE* ε4 status, alongside metabolic and vascular profiles, are increasingly recognized as key effect modifiers rather than trial exclusion criteria, while cardiometabolic risk factors themselves represent modifiable targets within precision-prevention frameworks. Precision-prevention does not imply narrowing eligibility, but rather stratifying risk to understand differential responsiveness. Without stratification, multidomain trials average across heterogeneous biological trajectories, washing out benefits that may be substantial in specific subgroups. With stratification, trials can identify who benefits, under what conditions, and at what intensity (15) (16).

Digital monitoring and delivery.

Advances in digital health technologies now allow objective, continuous measurement of behavior, adherence, and intervention dose through wearables and mobile platforms. This transforms lifestyle interventions from loosely defined exposures into quantifiable, adaptive treatments, while enabling scalable delivery beyond specialty centers (5) (17). Digital platforms also facilitate real-time feedback, adaptive support, and long-term engagement, features essential for prevention strategies that depend on sustained behavior change. To be effective, such systems should characterize lifestyle interventions, particularly physical activity, along multiple dimensions, including modality and diversity, rather than relying on single-dose representations that obscure meaningful variation in response (18).

Combination therapy paradigms.

Experience from cardiovascular disease, oncology, and HIV demonstrates that durable risk reduction in complex diseases typically requires coordinated, multimodal strategies rather than single interventions (19). Dementia prevention is no different. Lifestyle-based approaches have established feasibility and safety, while cardiometabolic risk has emerged as a biologically meaningful lever for intervention. Recent large trials evaluating semaglutide in early Alzheimer's disease, together with emerging emulated-trial evidence in diabetes populations, underscore both the promise and limitations of metabolic modulation when pursued in isolation (20) (21). Instead, future prevention efforts should evaluate pharmacologic agents as components of biologically informed, multidomain strategies, tested in clearly defined subpopulations, with careful attention to timing, route, dosing, and interaction with lifestyle interventions (22) (23).

Causal foundation models and multi-omic integration. Advances in machine learning now enable foundation models pretrained on large-scale multimodal biological data, shifting multi-omic research beyond associative biomarker discovery toward causal inference. Parallel progress in computational genomics, including accelerated sequence comparison, in-storage metagenomic processing, and optimized taxonomic classification, supports high-throughput microbiome analysis in complex clinical samples (24). Together, these advances allow integration of genomic, metabolomic, and microbial data with systematic perturbation experiments, enabling models that predict intervention effects rather than describe correlations. For dementia, such causal frameworks support stratification based on dynamic biological signatures, from gut-brain interactions to metabolic and neuroinflammatory pathways, adding mechanistic depth to risk prediction and enabling individualized prevention strategies (25).

A New Framework: Three Pillars of Precision-Prevention

To move dementia prevention from fragmented experimentation to sustained impact, future trials must be organized around a coherent framework that aligns biological insight, intervention delivery, and evidentiary rigor. We propose three interdependent pillars to guide the next generation of precision-prevention clinical trials (Figure 2).

Biology-anchored personalization.

Prevention strategies should be targeted according to individual risk profiles, considering genetic susceptibility, cardiometabolic status, biomarker evidence of neuropathology, and socio-economic and cultural context. Rather than treating heterogeneity as noise, trials should explicitly leverage stratification to identify effect modifiers and dose-response relationships (15) (16). Blood-based biomarkers can support earlier enrollment, enable interim biological readouts, and reduce reliance on late-stage cognitive decline as the sole outcome, increasing both efficiency and interpretability (3).

Multimodal, scalable delivery.

Effective prevention is unlikely to rely on a single intervention. Multidomain strategies combining lifestyle modification with targeted pharmacologic or nutraceutical components should be tailored to individual and regional realities (21). Digital platforms and community-based infrastructures can support monitoring, adherence, and adaptation at scale, ensuring that prevention is feasible beyond highly resourced research centers and applicable across diverse health systems (5) (6).

Rigorous design and harmonization.

Precision-prevention requires convergence in trial methodology. Harmonized cognitive and functional endpoints, standardized definitions of intervention intensity and adherence, and pre-specified stratification plans are essential for cross-trial comparability and pooled analyses (11) (26). Emerging analytic infrastructures, including agentic AI frameworks that coordinate inference across biological, behavioral, and contextual data streams, enable actionable insight from complex, multidomain trial designs. Adaptive and factorial designs further accelerate learning while minimizing participant burden.

Together, these elements transform prevention trials from isolated studies into a cumulative, globally informative evidence base.

What Needs to Happen Globally

For precision-prevention to move from experimental success to population-level impact, coordinated action beyond the research community is required. National health authorities should consider dementia risk reduction within healthcare and public health strategies, linking biomarker-informed risk assessment with structured, culturally adapted prevention pathways. This will require sustained investment in workforce training, digital infrastructure, and community-based delivery models so that prevention is not confined to specialized research centers.

At the international level, global and regional public health and regulatory bodies can play an important technical role by supporting convergence around prevention trial standards. Their contribution should focus on facilitating harmonization of outcomes, biomarker integration, and reporting of adherence and intervention intensity, rather than prescribing uniform models of care. Such an approach allows countries to adapt multidomain prevention strategies to local contexts while preserving scientific comparability and enabling pooled analyses across regions (27) (28).

Global scalability must be treated as a design requirement rather than a downstream consideration. By 2030, most new dementia cases will occur in low- and middle-income countries (29), yet access to biomarkers, digital tools, and long-duration trials remains limited. Priority investments include affordable blood-based biomarkers, shared trial platforms, and scalable digital systems that support monitoring and engagement in resource-constrained settings, alongside cost-effective implementation strategies (30).

Seizing the Precision-Prevention Moment

Dementia risk reduction stands at a decisive moment. The scientific foundations for multidomain approaches have been established, and new biomarkers, digital tools, and data-analytic approaches capable of integrating multidomain signals now make precision both feasible and scalable (8) (9) (15). The challenge is no longer whether prevention can work, but whether the field will organize itself to deliver decision-grade evidence that informs policy and practice. Advancing a harmonized precision-prevention framework requires alignment across researchers, national health authorities, global agencies, and funders. Without such coordination, effective interventions will remain fragmented and underutilized. With it, dementia prevention can evolve into a globally applicable strategy capable of reducing the burden of cognitive decline for decades to come (31) (32).

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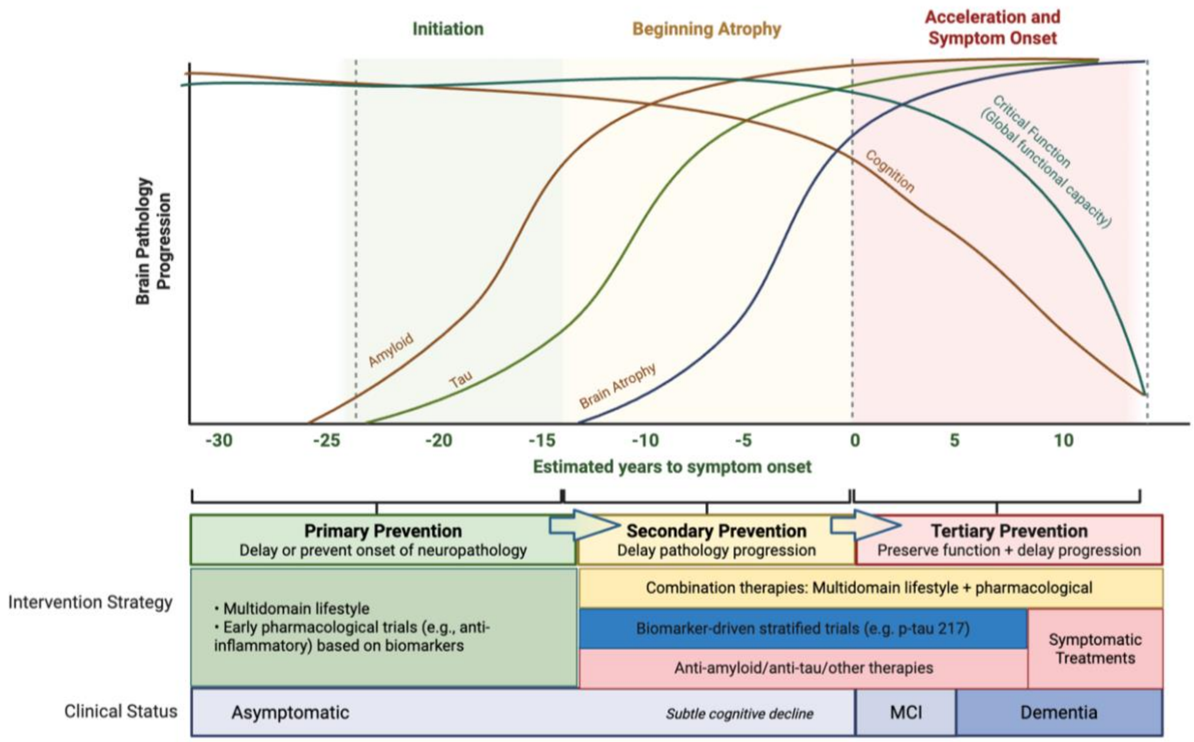
Box 1. Current Knowledge and Gaps in Dementia Prevention Research

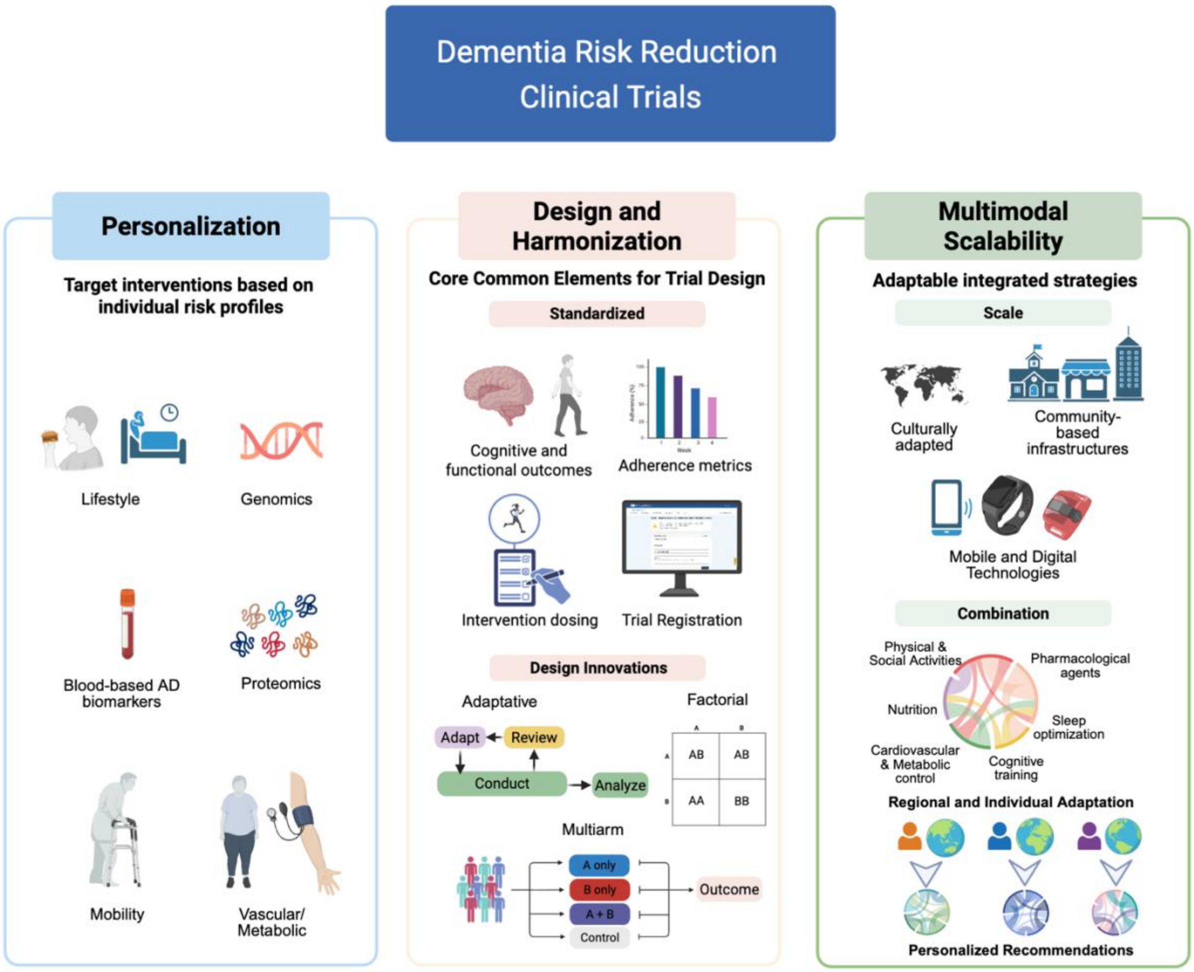
Question	Current Knowledge	Key Gaps
When is the ideal time to initiate intervention?	Life-course epidemiology and randomized trials indicate that midlife is a critical window for risk reduction, while later-life interventions can still modify trajectories, particularly among individuals with elevated vascular or metabolic risk [20,24,25]. Long-term follow-up from multidomain trials supports sustained benefit in selected populations [7,11,12].	The optimal biological risk/disease threshold for initiating intervention remains undefined. Trials rarely align timing to biomarker stage or cumulative risk profiles, limiting precision in identifying when specific individuals are most likely to benefit.
How long do the benefits last?	Short- and medium-term trials demonstrate improvements in cognition, cardiometabolic risk, and health behaviors over 2-3 years [7,8]. Emerging long-term follow-up data, including 11-year evidence from multidomain interventions, suggest persistence of some benefits beyond the active intervention period [11,12].	Evidence on long-term durability, need for booster interventions, and maintenance strategies across different ages and risk profiles remains limited. Most trials lack extended follow-up beyond five years.
What constitutes a "dose" in lifestyle trials?	Higher adherence and greater intervention intensity are consistently associated with stronger cognitive and health outcomes [10,11]. Digital tools increasingly allow objective measurement of activity, sleep, and engagement, enabling quantification of intervention dose [5,6].	There is no consensus on standardized dose metrics across intervention components or on equivalency between domains (e.g., physical activity vs cognitive training), limiting comparability and implementation guidance [10,13].
Which combinations yield synergistic effects?	Multidomain interventions likely outperform single-domain approaches, and combination strategies integrating lifestyle with pharmacologic or nutraceutical components are biologically plausible and increasingly tested [9,18,19].	Structured evaluation of combinations remains limited. Few trials are designed to test interaction effects, sequencing, or optimal pairing of lifestyle and pharmacologic strategies.
What drives individual responsiveness?	Genetic susceptibility, metabolic and vascular status, baseline cognitive reserve, and social factors influence intervention response [13,14]. Precision approaches such as individualized risk profiling have been shown to improve adherence and outcomes in selected trials [12,14].	Trials rarely incorporate stratification or are powered to identify effect modifiers. The causal pathways linking biological profiles to differential response remain incompletely characterized.

Figure 1. Timing dementia prevention trials across the disease continuum to enable precision-prevention



Distinct neuropathology progression trajectories, including amyloid, tau, vascular, and neuroinflammatory processes across Alzheimer's and related dementias, define critical windows for preventive intervention. Primary, secondary, and tertiary prevention strategies must be aligned to risk/disease stage, but also increasingly tailored to individual biomarker profiles to maximize intervention effectiveness (see Figure 2). MCI: Mild Cognitive Impairment; ptau 217: Phosphorylated tau 217; Aβ deposition: Amyloid β deposition.

Figure 2. **Pillars of Precision-Prevention Clinical Trials for Dementia Risk Reduction**



Future dementia risk reduction trials must integrate three core pillars: personalization based on individual biomarker-informed risk profiles, standardized trial design and harmonization of outcomes and adherence metrics, and scalable multimodal interventions tailored to diverse populations. Together, these elements provide a framework for building globally applicable, biologically informed, and sustainable dementia risk reduction strategies.