Primary Prevention of Dementia: The Future of Population-Based Multidomain Lifestyle Interventions

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Dementia affects 46.8 million of the world's population, and is projected to increase to 131.5 million by 2050 (1). Increasingly, with no available disease-modifying drug or cure for the disease, preventive strategies are being pursued to curb the worldwide epidemic. Accumulating evidence supports the importance of dementia prevention, with seven risk factors (diabetes mellitus, midlife obesity, midlife hypertension, physical inactivity, depression, smoking, and low education) estimated to contribute to 9.6 million cases, equivalent to a third of Alzheimer's disease worldwide (2). The potential public health impact of prevention is huge as a 20% reduction per decade from 2010 in the prevalence of these risk factors would translate to a 16.3% (1.5 million) reduction in dementia prevalence by 2050.

Primary prevention that focuses on approaches to prevent or delay the onset of cognitive impairment and dementia has gained increasing attention with the identification of potentially modifiable risk factors. These include vascular risk factors, such as smoking, hypertension, diabetes mellitus, and obesity (3). Also, physical activity, healthy diet, cognitive training, moderate alcohol consumption, and social participation have been reported to enhance cognitive ability and reduce the risk of cognitive decline and dementia. The majority of the findings, however, is based on prospective observational studies, and evidence on the effectiveness of interventions, mostly of single-domain, in primary prevention is weak (4). Targeting multiple risk factors is likely to engender cognitive benefit as risk factors of dementia often co-occur, with multiple healthy lifestyle factors contributing to improved cognitive function (5).

Previous clinical trials to prevent dementia have been limited by a single-intervention approach, inadequate sample size, short duration of treatment and follow-up, and inappropriate timing of the intervention (6). Taking lessons from these earlier trials, more recently, large-scale multicomponent interventions have been initiated. These include the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the Multidomain Alzheimer Preventive Trial (MAPT), and the Prevention of Dementia by Intensive

Vascular Care (preDIVA). These trials advocate a multidomain approach by promoting multiple lifestyle changes and active management of vascular risk factors and conditions.

In the FINGER trial, interventions consisted of nutritional counseling, physical exercise, cognitive training, and monitoring with management of metabolic and vascular risk factors. A significant benefit was observed in the overall cognitive performance and, more specifically, in the executive functioning and processing speed at 2-year follow-up (7). The MAPT, where omega-3 polyunsaturated fatty acid supplements were combined with multidomain intervention (cognitive training, physical activity, and nutritional advice), did not find significant effects on cognitive decline over 3 years (8). PreDIVA, a 6-year trial of nurse-led intensive vascular care addressing physical activity, smoking, nutrition, and vascular risk management, did not result in a reduced incidence of dementia (9).

It may come as somewhat of a disappointment that not all multidomain prevention trials produced positive results. It raises several issues to consider in the design and conduct of multidomain primary prevention trials.

Targeting the right population for intervention is a major challenge. Trials that administered combined interventions to those at high risk tended to yield more favorable results. To be eligible for the FINGER trial participants were required to have a CAIDE (Cardiovascular Risk Factors, Aging, and Dementia) score (based on age, sex, education, systolic blood pressure, body mass index, total cholesterol, and physical activity) of 6 points or higher. In the MAPT, subgroup analyses of those with a CAIDE risk score of 6 or greater and those with a positive amyloid PET scan revealed multidomain interventions to slow cognitive decline. In contrast, in preDIVA, to be eligible participants only had to be without dementia and disorders hindering long-term follow-up and, therefore, were not screened for an increased cardiovascular risk. These suggest that targeting those with a high vascular risk would be important to produce significant effects. Moreover, socioeconomically vulnerable segments of the population are likely to be at higher risk and may benefit from

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these interventions. Although low education was taken into account in calculating the CAIDE dementia risk score, education by itself does not adequately reflect the individual's socioeconomic position. Socioeconomic status, such as education, living conditions, occupation, income, and wealth, throughout the life course is cumulative, being associated with an increased risk of cognitive impairment and incident dementia in later life (10-12). It may be important to better identify and administer future interventions to those at the lower social gradient where small improvements in lifestyle risks are likely to obtain greater effects.

A difficult problem for primary prevention trials is identifying participants free of dementia to be included in the study. The risk score approach cannot discern those in the earliest stage of the disease from those without the disease. Targeting high risk groups most likely to benefit for prevention trials in the future may consider biomarker enrichment strategies (13). Employing a biomarker-guided approach (14) may aid in distinguishing the cognitively healthy group from those asymptomatic patients in the early preclinical stage. This would help to better delineate the effects of primary prevention from secondary prevention trials. However, to be feasible for large-scale trials, measurement of biomarkers would need to be less time-consuming and affordable. One caveat is that the selected, highly specific population group may limit the generalizability of the findings.

Closely tied to targeting population groups is the timing of the intervention. Risk factors are known to differentially operate at various stages of life, where finding the "the window of opportunity" is critical for exacting change and maximizing impact. Vascular risk factors of dementia, such as hypertension and obesity, are often present in midlife. Lifestyle habits such as physical inactivity and unhealthy diet, risk factors for vascular disorders, form in early life and their influence accumulate over the life course. Current trials are still limited in that they target risk factors in late life. Longer trials are needed that encompass interventions through several critical stages in life, but would be difficult to implement. A feasible option would be to design prospective cohort studies that incorporate clinical trials. FINGER is unique in that the trial participants were part of population-based surveys, making it possible to incorporate retrospective data on lifestyle and vascular risk factors. This type of integration of cohort and intervention studies should be encouraged, as it would further help to identify population at risk based on longitudinal information, and design effective interventions attuned to specific stages in the life course. Moreover, assessment of long-term outcomes, such as incident dementia, would become feasible. Linkages with health insurance claims and other data registries may provide further opportunity to this end.

External validity is always an issue for randomized controlled trials, and replications in other regions are

instrumental in giving credence to the early findings. Though not identical in design and scope, community-based, multidomain interventions studies are emerging in Asia. The Ohbu Study of Health Promotion of the Elderly (OSHPE) in Japan reported cognitive improvement and reduction in brain cortical atrophy, based on a multicomponent exercise program ("cognicise") that included physical activity, cognitive training, and social interactions for those with mild cognitive impairment who were considered to be at risk of dementia (15). In South Korea, an 18-month trial involving multidomain lifestyle (physical, cognitive and social activity, not smoking, alcohol drinking in moderation, and healthy diet) counseling through case management and home visits was implemented to healthy older residents by community health workers, resulting in a better maintenance of cognitive function (16). These provide evidence to support developing and applying dementia prevention strategies suitable to different cultures.

Multidomain interventions have proved somewhat effective, but are still limited in its impact. Because even small changes extended to the population level over time would accrue greater benefit, more practical and personalized strategies may help to enhance positive outcomes. In MAPT, a single-compound approach has not induced much benefit. Alternatively, multiple supplements or interventions to promote healthy dietary patterns, such as the Mediterranean diet, may prove to be more effective and long-lasting. With technological advances, internet-based programs offer new, practical approaches. In Australia, the Body Brain Life (BBL) study implements a population-based, low-cost intervention with online modules, including dementia literacy, risk factor education, engagement in physical, social, and cognitive lifestyles, nutrition, and health monitoring (17). The FINGER, MAPT, and preDIVA research groups have joined forces through the European Dementia Prevention Initiative (EDPI) to enhance data sharing and resources, fostering the design and development of new dementia prevention trials for the future (18). The Healthy Ageing through Internet Counseling in the Elderly (HATICE) which is part of the EDPI is examining the effect of a coach-supported interactive internet platform for the self-management of vascular risk factors (19). Engaging in a combined physical, cognitive, and social activity in "real-world" settings is also a practical strategy that may help enhance cognitive ability. In a randomized controlled trial of participants in the Experience Corps, an elementary school-based volunteer activity program for seniors, has been shown to improve executive function and memory (20). This type of participatory "health promotion" interventions are likely to be adopted in the community and sustainable in the long-term, with high public health relevance.

There has been a major paradigm shift in the understanding and management of dementia, with an emphasis on prevention (21). Population-based,

multidomain primary prevention trials have come to the forefront as a pragmatic approach to postpone or delay cognitive decline and dementia onset. Although positive results have emerged, methodological challenges abound. Innovative approaches are warranted with considerations on targeting high risk groups throughout the person's life course, implementing individualized interventions with sufficiently long durations, assessing long-term outcomes, and utilizing longitudinal and secondary data sources. There is a growing need to develop optimal preventive strategies throughout the life course that can be easily adopted and translated in the community to reduce the future incidence of dementia.

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