# Prevention of Late Onset Dementia: Moving from Randomized Trials to Public Health Intervention.

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**Existing paradigms for translation of evidence to public health intervention.**

A common paradigm used to translate research knowledge into public health implementation is the following: findings in observational studies support or lead to hypotheses about risk factors for disease. The plausibility of these hypotheses may be supported by basic science. With data from observational studies and basic science interventions are designed. In the case of drugs, these are tested in Phase I trials for preliminary data on safety and dosage, in Phase II trials for further data on safety, feasibility and efficacy, and Phase III trials for proof of efficacy. After phase III trials, public health interventions are implemented. However, randomized trials have important limitations[1]. First, results of randomized trials are an average of effects for winners, losers, and those who are indifferent to the intervention. Few major winners could skew the mean effect and create the false appearance of a significant public health benefit. Secondly, clinical trials are difficult to replicate in real world settings. Randomized trials' interventions are usually highly structured and costly, and thus difficult to translate into real world settings. Clinical trial samples are highly selected, and their results may not be generalizable. The concepts of efficacy and effectiveness are important in this context. Efficacy is the effect of an intervention under ideal conditions. Effectiveness is the effect of an intervention with proven efficacy in real world settings. These concepts are central to the field of comparative effectiveness research(CER)[2], which could be defined as the direct comparison of existing interventions to determine which work best for whom and which pose the greatest benefits and harms. An ideal paradigm to translate clinical trials to public health intervention is to obtain proof of efficacy, then obtain proof of effectiveness in real world settings, proceed to public health implementation, and then conduct surveillance of the effects of the public health implementation.

**Challenges in implementation of dementia prevention.**

Proof of efficacy. The main challenge to dementia prevention is that evidence on efficacy is limited or absent. A recent consensus statement from National Institutes of Health in the United States stated that "Currently, firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer's disease. …Evidence is insufficient to support the use of pharmaceutical agents or dietary supplements to prevent cognitive decline or Alzheimer's disease."[3] Most evidence suggestive of prevention comes from observational studies and basic science, and does not meet the criterion of proof of efficacy. Clinical trials testing strategies for the prevention of dementia need very large sample sizes and relatively long observation times, making them extremely expensive and difficult to conduct. There are several ways to overcome this. One is by using biomarkers as intermediate proxies of disease to decrease sample size and observation time, but this paradigm is controversial. Another strategy is adding cognitive measures as secondary outcomes to clinical trials, and this is an increasing practice. However, evidence of benefit for secondary outcomes has caveats, could be due to chance, and may need another trial with the cognitive outcome as a primary outcome to prove an initial finding.

Competition with other outcomes: a common axiom in cognitive impairment research these days is that “what is good for the heart is good for the brain”, mainly based on observational studies. These studies have shown that cardiovascular risk factors such as hypertension, obesity, diabetes, insulin resistance, dyslipidemia are associated with a higher risk of dementia. This has ethical and practical implications. If we know of effective interventions for the primary and secondary prevention of heart disease and stroke (which we do), is it ethical to test them for the primary and secondary prevention of cognitive impairment? If we know that interventions are good for heart disease and stroke risk independent of cognitive benefits, why test them at all? These considerations limit testing cardiovascular interventions for the primary and secondary prevention of cognitive impairment. However, many questions that are pertinent to cognitive impairment remain that need research. For example, it is not known if vigorous hypertension treatment in elderly persons may decrease brain perfusion and increase the risk of cognitive impairment. It seems reasonable to suggest that known interventions (e.g. for cardiovascular disease and cancer prevention) should be tested for cognitive benefits particularly when there is a concern for cognitive harm in susceptible populations.

Lifecourse challenges: Dementia and cognitive impairment in general have long and complex causal pathways. Putative risk factors for dementia such as hypertension, obesity, and dyslipidemia change over time, and could have a narrow “therapeutic window”. In addition, brain physiology changes over time, and interventions may have different effects at different points in the lifecourse (e.g. hypertension treatment on brain perfusion). Aging is related to the addition of new sources of disability, conditions, and medications that can modify the effect of an intervention for the prevention of dementia. From a public health perspective, this complexity puts stresses on the health care system.

**Case study: Prevention of diabetes as a strategy for the prevention of dementia.**

The observation that insulin resistance and type 2 diabetes are associated with a higher risk of dementia led to the hypothesis that decreasing insulin resistance and preventing type 2 diabetes could prevent dementia[4]. On this basis, the Diabetes Prevention Program (DPP) Outcomes Study (DPPOS) (ClinicalTrials.gov Identifier: NCT00038727) added a neurocognitive battery as a secondary outcome in 2009. The DPPOS is the observational phase of a clinical trial of metformin, lifestyle intervention (diet and exercise) vs. placebo. The DPP showed that metformin and lifestyle interventions were effective in preventing type 2 diabetes [5]. Relating the DPPOS interventions with cognitive outcomes could allow making inferences about treatment effects that have many caveats. The possible results for the cognitive outcomes in DPPOS are that there is no evidence of cognitive effect, that there is evidence of cognitive benefit, or that there is evidence of harm. Any result will be hampered by the fact that cognition is a secondary outcome, and by the fact that the DPPOS is likely to be implemented using CER principles independent of its cognitive effects. However, the DPPOS will provide data to understand mechanism of effect, and to conduct post-hoc analyses that may shed light on who is more likely to benefit or harm from a cognitive standpoint, and what DPPOS processes are responsible for the benefits or harms. If cognitive outcomes are measured in studies of CER of DPPOS, we will further be able to identify winners, losers, and indifferent, and identify barriers and modifiers of the intervention from a cognitive standpoint. Finally, the finding of a cognitive benefit in addition to cardiovascular benefits could be a potent message that may sway public health officials and the public in implementing this kind of public health intervention.

**Recommendations: Moving from Randomized Trial to Public Health Intervention.**

Given considerations described in this article, it seems reasonable to classify public health interventions for dementia prevention in 2 types: 1) General public health interventions (e.g. for cardiovascular disease or cancer) with possible or probable cognitive benefits; 2) public health interventions that are specific to dementia prevention. Examples of general public health interventions are dietary interventions, exercise, and interventions that seek to decrease cardiovascular disease in general. Examples of possible interventions that are specific to dementia prevention could be particular supplements or pharmacologic agents, mental exercise, and multidomain interventions specifically geared to improving brain health and preventing dementia.
It seems unlikely that there will be randomized trials of existing interventions with dementia prevention as a primary goal. It seems more likely that evidence supporting the use of existing interventions for dementia prevention will come from observational studies or clinical trials in which cognition is a secondary outcome. These general interventions with possible or probable cognitive benefit are likely to be implemented for other goals such as prevention of cancer or cardiovascular disease. It seems reasonable to suggest that public health entities conduct surveillance of cognitive outcomes (e.g. dementia diagnosis in administrative datasets) to further support the cognitive benefits of these interventions, to identify winners and losers, to identify barriers, key process components that are responsible for benefit, and modifiers of benefit or harm. This surveillance could also help estimate cost-effectiveness of these interventions taking into account the costs related to dementia in addition to their original target (e.g. cardiovascular disease). These revised estimates could help policy makers in prioritizing health care funds for interventions that improve health in several domains including cognition. This proposed surveillance is limited by inherent bias, confounding, and chance, and would require the refinement of existing epidemiological methods and perhaps development of new ones.

Interventions that are specifically geared towards dementia prevention should apply CER principles that lead to public health implementation. That is, once efficacy is established, winners, losers, indifferent, and doomed should be identified to refine the target population. Barriers, optimal doses, modifiers, and key components of interventions should also be identified. Then, effectiveness should be tested in real world settings. If effectiveness is proven, public health interventions should be implemented followed by surveillance.

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