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THE PREVENTION OF ALZHEIMER'S DISEASE: LESSONS LEARNED AND APPLIED

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Abstract

Alzheimer's disease (AD) affects over 5 million Americans with substantial consequences to patients, families and society that will only continue to be a significant cause of morbidity, mortality, and healthcare costs. With disease-modifying treatment trials unsuccessful at the present time and only symptomatic medications available, an emerging approach is the creation of prevention trials. Advances in diagnostic criteria, biomarker development and improved understanding of the biophysiological basis of AD make these initiatives feasible. Ongoing pharmacological trials using anti-amyloid therapies are underway in sporadic and genetic forms of AD. However, a large number of modifiable risk factors for AD have been identified in observational studies, many of which do not appear to exert effects via amyloid or tau. This suggests that prevention studies focusing on risk reduction and lifestyle modification may offer additional benefits. Rather than relying solely on large sample, long duration randomized clinical trial designs; a precision medicine approach using N-of-1 trials may provide more rapid results on whether personalized prevention plans can improve patient-centered outcomes. As there appear to be multiple pathways to develop AD, there may also be multiple ways to prevent or delay the onset of AD. Even if these precision approaches alone are not successful in preventing AD, they may greatly improve the likelihood of amyloid- or tau-specific therapies to reach their endpoints by reducing co-morbidities. Keeping this in mind, dementia may be as a disorder that develops over a lifetime, with individualized ways to build a better brain as we age.

Keywords

Alzheimer's disease; dementia; prevention; lifestyle; risk reduction; precision medicine; N-of-1 trials

INTRODUCTION

Alzheimer's disease (AD) affects over 5 million Americans with substantial costs to patients, families and society.[1] Projections by the Alzheimer Association anticipate if nothing is done, by the year 2050 there will be over 16 million cases of AD in the United States, and over 60 million cases worldwide. Over the past 25 years, only five symptomatic

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medications have met their endpoints in Phase III clinical trials and successfully come to market; of these, four are still available. Since 2003, every both symptomatic and disease-modifying agent has failed in Phase II/III due to challenges with safety and/or efficacy. This led to a bold initiative put forth by the National Alzheimer Plan Act to develop a disease-modifying treatment (DMT) by the year 2025.[2] Two important concepts are associated with this target date. First, if a DMT is to make it to market by 2025, then only medications that have already entered Phase II testing can reach this target date.[2] Second, if a DMT were available by 2025, then the 2050 projection of 16 million Americans with AD would be reduced by 5.7 million cases with societal savings of $367 Billion.[1] To complement efforts to develop a DMT for individuals with symptomatic AD, a concerted effort is underway to initiate preventive measures in asymptomatic individuals. Such efforts are also consistent the 2025 target goal.

An important question however, is whether AD can be prevented. To date, a large number of risk factors (Table 1), both modifiable (e.g., exposures, lifestyle and social habits) and non-modifiable (e.g., age, sex, genetics) have been identified. Recent revisions to the clinical criteria for AD[3] and mild cognitive impairment (MCI)[4] helped clarify the role of biomarkers in defining the pathologic cascade, and the addition of research criteria for presymptomatic disease[5] sets the stage for better modeling of the preclinical and prodromal stages of disease.[6] Efforts developing and validating fluid and imaging biomarkers now make it possible to explore underlying pathologic changes in amyloid, tau, dopamine transport, inflammation, signaling pathways, and someday alpha-synuclein and TDP-43 in symptomatic, prodromal, and presymptomatic individuals. Advances in genetic, epigenetic, and “omic” (e.g., proteomics, lipidomics, metabolomics) approaches will permit the modeling of transcriptional, translational, and post-translational changes. Furthermore, precision medicine approaches with demonstrable benefits in oncology are being applied to neurodegenerative disorders. Thus, the platform is in place to begin prevention initiatives.

These efforts have a great potential for both pharmaceutical and non-pharmacological approaches with earlier identification of at-risk individuals, expanding opportunities for faster and earlier diagnoses, better stratification of at-risk patients, higher enrollment into randomized clinical trials (RCTs) by reducing screen failure rates, and eventually more effective treatments. While the focus of this article will be on AD, the principles discussed here are relevant to related neurodegenerative disorders (e.g., Parkinson’s disease, Lewy body dementia, vascular dementia). Assuming curing AD remains a substantial unsolved challenge, preventing or simply delaying the dementia onset could significantly change the face of disease.

PHARMACOLOGIC APPROACHES TO PREVENTION

A number of prevention studies are ongoing in both sporadic and autosomal dominant forms of AD. Results are still pending but a review of ClinicalTrials.gov[7] provides important details about these studies. One such study is the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s (A4) recruiting individuals aged 65–86 with normal cognitive function but positive AD biomarkers (amyloid deposition by PET scan). These individuals are followed for three years of treatment with an anti-amyloid monoclonal antibody. The Alzheimer

Prevention Initiative (API) will study individuals age 60–75 with normal cognition who have two copies of the ApoE e4 allele, putting them at a high risk of AD. These individuals are for two years of treatment with a different anti-amyloid monoclonal antibody. The TOMMORROW Study will enroll individuals age 65–83 with normal cognition who have a polymorphism of TOMM40 gene associated with increased risk of AD. Individuals are followed for five years of treatment with pioglitazone, an anti-diabetes drug. In parallel to these trials in sporadic cases with enhanced risk, trials are ongoing in individuals with autosomal dominant forms of AD including the API and Dominantly Inherited Alzheimer Network – Treatment Unit (DIAN-TU) using monoclonal antibodies. A particular advantage of the trials in familial AD is that age of onset is predictable so that if a DMT effect exists, it is more likely to be detected. A potential disadvantage of these trials is whether the results are generalizable to the much more common sporadic forms where risk factors other than genetics may predominate.

Similar to prevention trials, there are number of prodromal studies with a major focus on individuals with MCI. Results are still pending for many of these trials but at least one Phase II study had promising results. Aducanumab immunotherapy[8] against the amyloid protein not only demonstrated changes in CSF amyloid over 54 weeks in a dose-dependent manner but also demonstrated significant changes in cognitive and functional measures. These findings support the concept that there may be a critical window for these agents to be administered in order to increase the likelihood of success.

LIFESTYLE MODIFICATION INTERVENTIONS

Modifiable Lifestyle Factors

A number of modifiable risk and preventive factors for AD have been described in observational studies (Table 1). Across several studies, prominent risk factors include diabetes, hypertension, renal dysfunction, alcohol and smoking patterns, high cholesterol, coronary heart disease, depression, sedentary life style, low cognitive activity, and diet. These factors combined account for >50% of the attributable risk for AD.[9] The most difficult of these factors to address is diet as it is highly dependent on income and access to fresh foods.[10] In a 16-year observational study of 949 individuals using the Lifestyle for Brain Health (LIBRA) measure of modifiable risk factors, a 1-point increase in LIBRA scores was associated with a 19% increased risk of dementia.[11] In a meta-analyses of 19 studies on cognitive leisure activities[12] including crossword puzzles, card games, computer use, arts and crafts, life-long learning, group discussions, and music had a protective effect (odds ratio=0.58). In addition, physical activities may lead to a 20–65% risk reduction depending on the type and intensity of activity through mechanisms involving reduced vascular disease risk, improved respiratory function, stimulation of trophic factors, and reduced oxidative stress and inflammation.[13] Objective measurement of midlife vascular risk factors demonstrated increase risk of dementia in late life.[14] In a study of 2000 individuals aged 71–78y, work-related stress increased the risk of MCI (odds ratio=1.38), dementia (odds ratio=1.53), and AD (odds ratio=1.55).[15]

In spite of the differences between countries of origin, culture, language, educational attainment, and ages studied, the aforementioned studies and many others are convergent for

a short list of risk factors that seem to play a critical role in the development or prevention of AD and related disorders. This consistency has led to the implementation of a number of dementia prevention initiatives to modify these risk factors, most of which cannot be directly linked to either amyloid or tau deposition.

Ongoing Prevention Initiatives

The European Prevention of AD (EPAD)[16] initiative is currently recruiting to examine whether alteration of risk factors for AD that occur in early- and mid-life potentiate pathophysiological changes decades before dementia onset. The Innovative Midlife Intervention for Dementia Deterrence (In-MINDD) trial[9] considers 11 identified risk factors (e.g., diabetes, hypertension, renal) that account for 50% of the attributable risk and enrolled 600 individuals to participate in an internet education intervention. To date, the largest initiative is the FINGER study[17] enrolling 1260 individuals in an educational intervention that includes modules in diet, exercise, cognitive training, and vascular risk reduction. Overall between-group differences reached statistical significance for global cognition, executive function, and processing speed but not episodic memory.[17] These results suggest that lifestyle modification may offer some benefit in cognitive function, albeit with a small effect size.

PRECISION MEDICINE APPROACHES TO PREVENTION

While age is the single greatest risk factor for AD, it is not inevitable. The best estimates suggest that at age 85, there is 42% risk of developing AD.[1] Of course, this means that 58% of older adults do not develop dementia, even if amyloid can be detected in the brain. The reasons are unknown, but may be explained in part by a host of modifiable and non-modifiable risk factors (Table 1). Up to 30% of AD cases may be preventable through modification of risk factors, and behavioral changes to mitigate the impact of those risk factors that are not modifiable.[18] There remains an ongoing debate as to whether the current evidence base is sufficient to initiate prevention programs because: (a) it is difficult to prove causation from observational studies, and (b) it is difficult to pool multiple RCTs due to differences in study design, measurements used, and anticipated outcomes.[18] While a well-balanced, healthy lifestyle may be the cornerstone of disease prevention and brain health, each individual risk factor (vascular, lifestyle choices, psychosocial) may act both independently and potentiate the effects of each other.[19,20] Therefore, a prevention initiative needs to be both multimodal, and tailored to address individual risks.

These requirements lead to a number of design and analytic challenges. Many prevention RCTs use time-to-event analytic strategies to demonstrate a DMT effect. Such designs are optimal when anticipated treatment effects remain constant over time, however in the case of dementia prevention this is unknown. Thus, time-to-event strategies such a hazard ratios may not be the best way to model effects, particularly if the detectable signal is a late effect of the intervention.[21] Since AD is quite heterogeneous in risk factors, age of onset, presentation, progression, and pathology burden, designing a study to treat individuals as a homogenous population requires large sample sizes (thousands to tens of thousands) to be followed for long periods of time (years to decades).[22] This markedly increases study costs,

staff burden, and participant burden. In the absence of robust biomarkers that mark disease onset and progression, rather than just the presence of pathology, RCT design will remain a challenge.[23] Barriers to prevention studies include: limited understanding of the real relationship between dementia risk factors and the impact of risk reduction; complexity of life course on dementia risk factors; lack of standardization of study design, definitions and outcomes; difficulty of translating RCT findings into real-world practice; cultural and social barriers to implementation; lack of research capacity to enroll large research cohorts for long periods of time; and pervasive social stigma associated with AD.[18]

Since effective prevention strategies remain elusive despite significant advances in our understanding of the biology and pathophysiology of AD, an alternative approach would be to take advantage of precision medicine designs used in oncology trials to tailor interventions to an individual's phenotypic and genotypic expression. With improved classification and phenotyping of patients, trial ready cohorts can be targeted more appropriately with interventions (both pharmacological and non-pharmacological) designed to ameliorate specific pathologic mechanisms, based on specific biomarkers and patient characteristics.[23] Future trials could then be created to more quickly determine efficacy and safety ("fast to fail") by moving away from one-size-fits-all approaches to patient-specific precision treatments.

This would also require re-thinking trial design for prevention measures, moving to more "N-of-1" designs. N-of-1 trials consider the individual patient as the sole unit of observation to study the efficacy and/or adverse impact of an intervention,[22] and are guided by objective data-driven criteria, while leveraging the study designs and statistical techniques common to RCTs.[22] Since risk and molecular profiles of AD vary widely by patient, grouping individuals into single entities (placebo vs. treatment-arm) may mix "super-responders" with "non-responders" washing out treatment effects that only become apparent in *post-hoc* analyses.[24] Instead, comparing time-to-disease progression of an individual patient using a novel therapeutic approach to the time-to-disease progression for that same patient for the immediately preceding treatment paradigm may be preferable.[25] N-of-1 trials may be less bound by threats to generalizability of large RCTs due to recruitment delays and challenges to translate significant p-values in large treatment groups to the care of an individual patient, which is the ultimate goal of clinical practice. In a meta-analyses of 70 N-of-1 trials, of 57 completed trials, 50 provided definitive clinical or statistical answers with 39% prompting physicians to change the plan of care.[26] Another meta-analysis examined 108 trials involving 2154 participants and found 54% of participants had subsequent treatment decisions changed based on the results.[27] To create the platform for such trials, several conditions must be met (Table 2). Patients must be deeply phenotyped with characterization of sociodemographic, psychological, clinical, cognitive, functional, biomarker, and genetic traits. Ideally, these patients would agree to be followed longitudinally, have samples banked for future analyses, and consent to autopsy to provide confirmation of both diagnosis and treatment effects on brain pathology. Statistical considerations may take advantage of both alternative time-series analyses and within- and between-subject comparisons. Lastly, an important caveat is the cost of care when a high-cost intervention is planned, for example off-label treatment with an expensive medication.[22]

EXAMPLE OF A PERSONALIZED MEDICINE APPROACH TO DEMENTIA PREVENTION

As an example of how this may applied in a pragmatic sense, we are developing N-of-1 trials to personalized dementia prevention using an evidence-base derived from an extensive literature review, and results of an NIH-funded project to conduct dementia screening in multicultural communities (R01 AG0402-11-A1, study design reviewed[28,29]). In addition to screening for cognitive impairment, broader medical screening for diabetes, hypertension, vascular risk factors, obesity, mobility, physical performance, frailty, and depression was incorporated into a "Healthy Body, Healthy Mind" approach to make the concept of dementia screening more acceptable, and to understand the impact of co-morbid disease on cognitive performance. This cross-sectional study confirmed many findings of observational studies regarding the association between cognitive performance and diabetes, hypertension, obesity, vascular risk factors, and depression while providing novel findings linking cognitive performance to sarcopenia[28] and mobility.[29] These collective findings were prospectively applied to develop N-of-1 trials. For example, a 68-year old college-educated woman (Note: although an actual case, some features were altered to preserve anonymity) presented with a 1-year history of subjective memory complaints (misplacing car keys, forgetting conversations, defensiveness about memory issues), but with independent functioning in her everyday activities. Her relevant past history is significant for hypertension and hypercholesterolemia. Her physical exam findings include mild hypertension (132/92) but normal cardiac and peripheral vascular exams. Pertinent neurologic findings include mild, symmetric weakness; decreased vibration sensation in the lower extremities; and mild postural instability. Cognitive testing revealed global deficits (Montreal Cognitive Assessment score 19/30), working memory and executive dysfunction, and episodic memory deficits on list learning that disappeared with cued recognition. Physical and functional testing revealed low lean muscle mass, at-risk nutritional status, modest daily physical activity, mild deficits on physical functionality (Short Physical Performance Battery score 7/12), and mild frailty (Fried Frailty Phenotype Score 3/5). Gait and balance testing revealed slowed gait speed (1.07 m/s), marked slowing (22.9%) with a dual-task challenge (walking while talking), and postural sway with eyes closed. Blood-based biomarkers revealed an abnormal lipid profile (elevated total, LDL- and non-HDL cholesterol; elevated LDL and small LDL particles; and reduced HDL particles), elevated inflammatory markers (hs-CRP and myeloperoxidase), ApoE 3/4 genotype, and evidence of insulin resistance (elevated fasting glucose, hemoglobin A1c, and estimated average glucose). Quantitative MRI revealed normal hippocampal size and lateral ventricle volume, however there were confluent white matter hyperintensities with frontal lobe predominance. Auditory event-related potentials demonstrated delayed median reaction times and reduced amplitude at the N200 peak (linked to impaired attention and executive function), and left-right asymmetry with frontal predominance (linked to vascular injury), but normal amplitudes and latencies at all other peaks, including the P50 peak associated with amyloid deposition.[30] This deep phenotypic evaluation provided actionable findings in cognitive testing (executive and working memory deficits with cued episodic memory improvements supporting intact hippocampal circuitry), physical testing (sarcopenia, at-risk nutritional status, poor physical functionality, and early frailty), gait testing (slowed gait speed,

impaired dual tasks, postural instability with eyes closed), biomarker testing (lipid profile, inflammation, insulin resistance, ApoE4 genotype suggesting poor response to statins), MRI (preservation of hippocampal and cortical volume, extensive white matter disease), and EEG (executive dysfunction and evidence of vascular injury) and supported a diagnosis of vascular cognitive impairment. A personalized treatment plan was then developed focusing on (a) dietary counseling (MIND diet, high protein snacks, glycemic control); (b) physical therapy for gait, balance, strengthening, and conditioning; (c) referral to a personal trainer for aerobic, resistance, and flexibility training; (d) mindfulness (yoga, meditation) for stress reduction; (e) cognitive exercise focusing on problem-solving skills, (f) omega-3 supplementation and possible resin therapy for cholesterol lowering; (g) improved blood pressure monitoring; and (h) initiation of a baby aspirin to improve blood flow. Longitudinal follow-up is needed to monitor adherence to recommendations and for evidence of improvement in outcomes. However, such a trial could provide a direct estimate of individual treatment effects, fine-tune personalized care plans, enhance precision of future treatment decisions, improve patient-centered outcomes, and if successful, reduce long-term healthcare costs.[25]

DISCUSSION

There is increasing evidence that multiple medical conditions increase the risk of neurodegeneration and subsequent development of dementia (Figure 1). Further, it is becoming clear that the majority of these risk factors act in amyloid- and tau-independent ways. Trials testing the amyloid hypothesis (β- and γ-secretase inhibitors, anti-aggregation medications, mono- and polyclonal antibody approaches), anti-inflammatory agents, and early-phase anti-tau therapies have failed to meet outcomes or have been discontinued due to safety concerns. While we wait for successful pharmacotherapy, we can take advantage of these multiple pathways leading to AD to test hypotheses around risk reduction and mitigation. In all likelihood, efforts to prevent cognitive decline and development of dementia may be more successful when multimodal and directed to at-risk individuals based on their personal health profile, rather than “one-size-fits-all” approaches. The detection of, and interventions addressing root causes may offer novel approaches to diagnosing, treating, curing, or preventing AD. AD offers a large array of potentially modifiable risk factors (lifestyle, exposure, environment, co-morbid disease) that are excellent targets to personalize the approach to medical care. Precision medicine approaches specifically target the heterogeneity of AD by identifying person-specific risk factors and applying a tailored intervention directed against this risk profile. Even if these precision approaches do not, in and of themselves, cure or prevent AD – removing other pathways to neurodegeneration may greatly improve the likelihood of amyloid- or tau-specific therapies to reach their endpoints. Perhaps it is time to abandon generalized approaches to AD, but rather consider neurodegenerative disorders as diseases of a lifetime, and that there may be individualized ways to build a better brain as we age.

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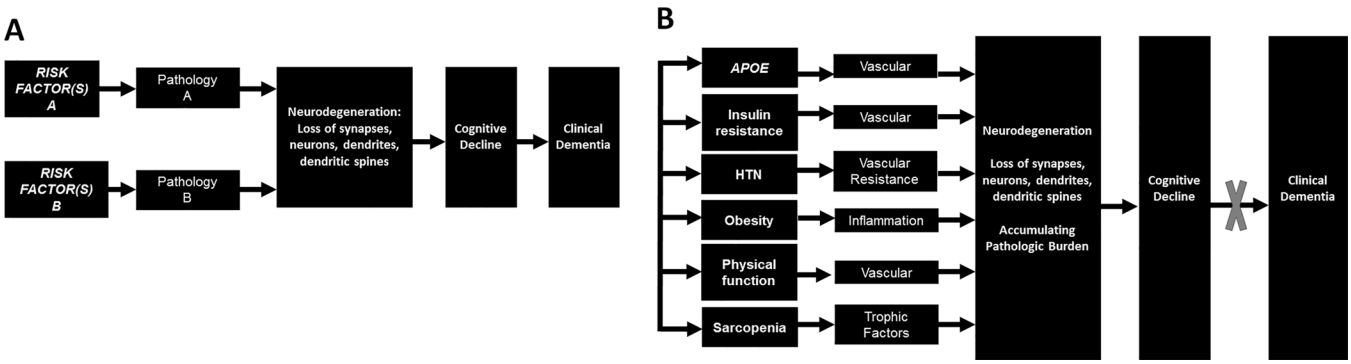

Figure 1. Model of a Dementia Prevention Initiative

Panel A: Hypothetical model of the development of clinical dementia. Prior to diagnosis, there would be evidence of cognitive decline, which reflects neurodegenerative changes including cellular dysfunction and loss, synaptic dysfunction, and loss of connectivity. Presumably, these downstream changes are caused by accumulation of one or more pathologies. If more than one pathology is present, then each pathology should have its own risk factor or factors (i.e., Risk Factor A causes Pathology A, while Risk Factor B causes Pathology B).

Panel B: Application of model in N-of-1 trial (described in detail in text). Six different risk factors were identified during the clinical evaluation presumably working through different pathways with the end result being neurodegeneration, cognitive decline, and if unchecked, eventually clinical dementia. A personalized prevention plan directed at root causes of impairment, if successful would prevent the conversion of cognitive decline to dementia (marked by X in Panel B). As root causes may interact or potentiate each other's effect on neurodegeneration (connecting arrows on the left side of Panel B), multimodal approaches are more likely to have an effect than singular approaches.

Table 1

Alzheimer's disease risk and protective factors

Risk Factors (Non-Modifiable)	**Protective Factors (Modifiable)**
Age	Cognitive reserve and mental activity
Sex	Educational attainment and lifelong learning
Family history	Cognitive leisure activities
Apolipoprotein E ε4 allele*	Physical activity and exercise
Risk Factors (Modifiable)	Social engagement
Diabetes and insulin resistance	Mindfulness and wellness activities
Obesity	Optimism and Purpose in life
Metabolic syndrome	Diet
Hypertension	Omega-3 intake
Hypercholesterolemia	
Cerebrovascular disease	
Depression	
Psychological and physiological stress	
Traumatic brain injury	
Sleep disordered breathing	
Smoking	
Alcohol abuse	

Note: ApoE is the major risk gene, a number of other minor risk genes have been identified

Table 2

Basic Principles of a Dementia Prevention Program

Establish a longitudinal cohort of individuals without memory impairment and with prodromal disease
Develop a protocol that can measure patient-centered and health-economic outcomes
Annual evaluation of clinical, cognitive, functional, and behavioral features
Collection and banking of biomarkers: blood, spinal fluid, DNA, cell lines, MRI, PET scans
Encourage autopsy participation
Deep phenotyping of individuals with near participation in all biomarker collection protocols
Application of precision medicine-type interventions to match treatment to individual characteristics
Test tailored N-of-1 interventions over a designated time period to determine whether protocols alter biophysiological profiles, disease-relevant biomarkers, and outcome measures
Statistical plan to incorporate immediate, intermediate, and long term time-to-event analyses
Create of trial ready cohort for larger scale pharmacologic and non-pharmacologic interventions