Several decades of comprehensive research have increased our understanding of Alzheimer’s disease (AD) to a certain extent; however, the knowledge accumulated thus far has not yet altered its epidemiological trajectory or underlying disease process [1,2]. In the absence of a clear avenue to advance, funding policies continue to support the research on AD with the expectation that the dilatory breakthrough will eventually emerge from innovative laboratory investigations. This general approach seems reasonably viable under the assumption that researchers have the necessary conditions for making groundbreaking discoveries. Alternatively, it may simply prolong a line of research that bears little relevance to public health.

In the journey for the AD cure, the quandary of necessary conditions began with seeking treatment for diagnosed patients without the capability of restoring the variable brain structures and functions that have atrophied over the course of the illness. In the absence of remedial options, the field is now shifting toward the development of preclinical interventions that aim to curb the neurodegenerative process of AD while the brain is still relatively well-preserved and changes to psychosocial functioning are either minimal or imperceptible [3,4]. The preventive approach obviates the barrier of neuronal regeneration. However, it still faces major impediments to progress, most critically, around identifying the covert incipience of AD pathogenesis [5,6].

In order to meet this challenge, the field has committed extensive resources to the study of biological markers. Although essential for the detection of preclinical pathology, biological markers suffer from major practical disadvantages. In the research setting, for example, the recruitment of asymptomatic participants to preclinical studies with amyloid imaging can be difficult to execute and cost-prohibitive across multiple trials. On the clinical front, the extent to which new drug discoveries may yield epidemiological gains depends largely on the presence of cost-effective technology that can detect preclinical AD in the community at large. Employing amyloid neuroimaging or even CSF-based procedures in routine preventive healthcare practices may not be sustainable from a practical perspective. Thus, significant progress toward AD prevention requires innovative measures that can effectively facilitate preclinical trials and ultimately identify appropriate treatment recipients in the general public.

One possible avenue to advance is to balance the investment in biological markers with the development of cognitive markers. From a practical perspective, cognitive markers can function as effective gatekeepers for invasive, labor-intensive and expensive biological procedures. In a conceptual view, cognitive markers target the insidious development of the core clinical feature of AD [7,8]. Since biological markers provide only partial prediction of the functional progression in AD [9], they should be employed in tandem with cognitive markers within a two-signal clinical model. In other words, preclinical AD may be determined with greater certainty if the accumulation of beta amyloid plaques is observed after an abnormal decline in cognitive functioning is established. In this light, the funding bodies of AD should consider a major longitudinal investment in the development of cognitive markers that can detect the departure from normal aging at the earliest possible point.

This endeavor requires a radical shift in the role that primary care plays in the diagnosis and treatment of dementia. At the moment, the brain seems to be largely absent from the checklist of standard physical exams during midlife, primarily due to a systemic reluctance to diagnose non-contagious conditions that have no cure [10]. This policy deprives the public of the various advantages of early diagnosis, and it also delays the progress of preventive research. The latter notion raises the question of whether it is feasible for AD researchers to find a preclinical cure for a disease that preventive healthcare practices deliberately ignore.

Incorporating cognitive markers to the routine practice of preventive health care can expand the scope of preclinical observations from small laboratory samples to the general population. There are about 5 million people in the United States who carry the diagnosis of AD [1]. Hence, the number of Americans who are currently in preclinical stages is, by implication, even higher. The integration of a cognitive maker to primary care during midlife, as a standard of care, can shed their anonymity and thereby dramatically change the conditions for advancing the research on AD prevention. This may be accomplished by incorporating to the annual physical exam a brief, electronic, self-administered “cognitive stress test” that assesses functional limits. In the Internet era, the data can accumulate longitudinal on a single server across many clinics with minimal labor.

The potential benefits of employing this procedure can be substantial. Most importantly, annual cognitive feedback can increase the motivation of high-risk patients for making protective lifestyle changes prior to the development of functional impairments. A midlife shift toward a healthy lifestyle is a disease-
modifying intervention and one of the most promising methods to date for preventing AD [11,12]; yet, behavioral prevention receives little attention relative to pharmacological alternatives.

The behavioral prevention of AD should attain greater emphasis because it probably targets major etiological factors. In recent years, there has been increasing skepticism about the amyloid cascade hypothesis [13], and a growing interest in the etiological role of oxidative stress [14]. There is compelling evidence that oxidative stress precedes the accumulation of beta amyloid deposits and increases the risk of AD, either by the dramatic effects of recurrent head trauma [15] or, more commonly, through the repeated micro-injuries that result from chronic allostatic overload [16]. In either case, whether the axe of stress cuts into the brain with few turbulent blows or a myriad of liminal strikes, the restoration challenge remains equally formidable; however, effective prevention, under a diathesis-stress paradigm, may become easier to attain. In this regard, the behavioral approach offers unique advantages. More specifically, behavioral interventions that effectively mitigate the neurotoxic effects of oxidative stress are well-known and feasible to implement [17]; whereas, pharmacological measures of stress inoculation for the human brain do not currently exist. Thus, even in modern times, a healthy lifestyle may still fundamentally provide the most effective protection against the “thousand natural, [and exceedingly unnatural], shocks that the human brain is heir to”. From this perspective, a cognitive marker may provide the required seismographic indication for activating the psychological mechanisms of behavioral prevention.

In conclusion, if primary care continues to wait for a biological cure before it embraces a cognitive marker for dementia, AD prevention may linger as a chimera in academic discussions for many years. To avoid further stagnation in AD prevention, funding policies should seek to maximize the effects of approaches with the greatest potential for practically assessing preclinical decline, and prioritize them over speculative paradigms that have less proximal relevance to public health. In this view, epidemiological progress in AD prevention may require funding policies to consider further diversifying their research portfolio. On the side of primary care, providing a wide platform for examining preclinical AD in the general population may increase public awareness in a manner that will set behavioral prevention into motion. With the proper infrastructure in place and heightened consumer demand in the lead, the biological breakthroughs will eventually follow. AD prevention, however, may not advance as quickly the other way around.

REFERENCES


