12 OVERVIEW

In the 1990s, I spoke at an Alzheimer's Association conference about my research on mental and physical activities and disease risk. At a press conference, I suggested that in order to lower the risk of Alzheimer's disease, people should be physically and mentally active throughout life, avoid smoking and obesity, eat a diet high in plant foods and low in saturated fat, and properly manage diabetes and hypertension. I explained how these recommendations were based on the work of my group as well as many others from around the world.

When I concluded my remarks, an Alzheimer's Association official stood up, raised his arms out wide and said, "Wait, Dr. Friedland's suggestions have not been verified in a placebo-controlled, double-blind randomized trial, and are premature."

I was dumbfounded. I responded by saying my recommendations were already known to be good for people anyway, and that currently available research already suggested that they would be helpful. Also, people who follow them (eat healthily, exercise, etc.) have no risk of side effects. It's true that some of the guidance recommendations listed in the following chapters have not been comprehensively evaluated using double-blind, placebo-controlled, randomized trials. It will be terrific when these studies are completed, but we need to know what to do now. But not everyone agrees with me.

In a 2010 "State-of-the-Science Conference statement: preventing Alzheimer's disease and cognitive decline,"

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researchers observed that diabetes, hyperlipidemia in midlife, and tobacco use were associated with an increased risk of Alzheimer's disease.[114] Mediterranean diet, folic acid intake, low or moderate alcohol intake, cognitive activities, and physical activities were associated with decreased risk. However, because the "quality of evidence was low for all of these associations" they were unable to draw firm conclusions on the association of any modifiable factors with the risk of Alzheimer's disease.[114,115]

In 2017, the US National Academies of Science, Engineering and Medicine led by Alan Leshner, CEO emeritus of the American Association for the Advancement of Science, and Story Landis, Director Emeritus of the National Institute of Neurological Disease and Stroke, also argued that the data were too weak to issue specific guidelines to the general public concerning what people can do to lower the risk of Alzheimer's disease.[116]

I strongly object to these conclusions. I met Shivani Nandi at a 1999 meeting of Alzheimer Disease International in Johannesburg, South Africa. We fell in love and married. Since we're both devoted to helping people avoid Alzheimer's disease, we collaborated on a paper published in 2013. Our satirical essay, "A modest proposal for a longitudinal study of dementia prevention (with apologies to Jonathan Swift, 1729)" in the *Journal of Alzheimer's Disease* focuses attention on the need for Alzheimer's disease prevention efforts.[34] We proposed a plan for a 40-year study of 10,000 people randomly assigned to groups of low- or high-saturated fat in the diet, head injury, high or low levels of mental and physical activity or inactivity, as well as smoking or non-smoking. Such a study is clearly impossible to conduct. Our point is that since this ideal study can't be accomplished, we must proceed with recommendations based on available evidence. It's simply not acceptable to wait for further information before recommendations can be made. Our "modest proposal" illustrates that the absence

of definitive evidence should not restrict us from making reasonable recommendations based on the evidence that is already established. As the American astronomer and author Carl Sagan said, "The absence of evidence is not evidence of absence."

We know that hypertension and smoking are both risk factors for dementia. (We also know that they are risk factors for heart disease and stroke, as well as other conditions.) Why was it not recommended by the eminent panels that government and institutional bodies encourage better management of hypertension and avoidance of smoking in order to lower the dementia risk? What is the possible danger of such a recommendation? It has been estimated that risk factor reductions (similar to the ones I am recommending to you) could diminish the prevalence of Alzheimer's disease by 10 percent worldwide and 25 percent in the United States. About half of all Alzheimer's cases are thought to be potentially attributable to hypertension and smoking.

A recent analysis of 153 randomized clinical trials suggests the following factors may increase the risk of Alzheimer's disease:[117]

- low levels of education,
- low levels of cognitive activity (mental stimulation),
- low levels of physical exercise,
- low intake of vitamin C,
- high blood homocysteine levels,
- depression,
- stress,
- diabetes,
- head trauma,
- hypertension in midlife,
- obesity in midlife,
- significant weight loss in late life,
- smoking,

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- poor sleep,
- cerebrovascular disease,
- frailty, and
- atrial fibrillation.

Before we consider how to implement recommendations concerning these risk factors, we must consider carefully the context of aging. An important aspect of these risk/protective factor considerations is that they involve several conditions, not only Alzheimer's disease. Hypertension, midlife physical inactivity, midlife obesity, and smoking are all risk factors for Alzheimer's disease, but they are also risk factors for cardiovascular disease and stroke. These conditions are linked to Alzheimer's disease itself: persons with heart disease and cerebrovascular disease are at a greater risk of Alzheimer's disease because heart disease and stroke reduce a person's physical reserve capacity and make it more likely that dementia will appear in the early stages of degenerative disease. Heart disease and stroke accelerate the Alzheimer's process in the brain. Red meat and low fiber intake are both risk factors for colon cancer. It is wise for me to offer these recommendations, and for you to heed them, because they are clearly beneficial to human health. Four factors are critical.

1. **Risk and protective factors operate over a lifetime.** With Carol Brayne of the University of Cambridge, I addressed these issues in a paper titled, "What does the pediatrician need to know about Alzheimer's disease?"[118] Early-life cognitive enrichment is associated with favorable cognitive health in late life, demonstrating clearly that preventive measures should be started as early as possible.[22] One main reason why there are no placebo-controlled, randomized trials to evaluate the influence of early-life factors is that they cannot be done; a clinical trial cannot be done over a 40-year period. Results of trials that show no benefit

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over a three-year period do not mean that the intervention will not be effective if applied for a longer time.

The lifestyle factors reviewed in the following chapters apply to all phases of the life cycle, including the very early years. In a remarkable series of experiments, Michael Meaney and colleagues in Montreal have shown that maternal affection alters the packaging of genes in the hippocampus of baby rodents.[I] Animals who receive more maternal affection have more receptors on neurons in the hippocampus that are important for memory and learning.[119] They showed that animals receiving more maternal affection had a faster resolution of the stress response, improving survival of neurons and memory with aging. The beneficial effects of the mother's interaction with the baby have been assumed to be created through influences on the stress response. It may also be a result of the impact of the maternal contact on the baby's developing microbiota. There is a large literature showing that intimate contact between human mothers and babies is good for physical and psychological development.

The importance of children's exposure to microbes has been emphasized in a recent book from microbiota experts Jack Gilbert and Rob Knight. In their book *Dirt Is Good: The Advantage of Germs for Your Child's Developing Immune Syste*m, they note that children who grow up with a dog have more competent immune systems than children who do not.[120]

2. **Alzheimer's disease takes several decades to develop and happens late in life. So our goal is not only to prevent it from developing, but also to delay its onset.** It is estimated that if the onset age of Alzheimer's disease can be delayed by five years the prevalence will be cut in

[I] This mechanism of gene alteration involves epigenetics, heritable changes in gene expression that do not involve changes to the DNA sequence.

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half. By increasing the fitness of body systems which interact with the brain, as well as enhancing the fitness of the brain itself, we have the opportunity to alter disease processes over the course of a lifetime to delay the onset of dementia.[121]

3. **Environmental factors matter.** Recent studies have shown that the incidence and prevalence of Alzheimer's disease has dropped by about 20 percent in the past two decades (corrected for the fact that there are more older persons), according to studies in Europe, Asia, and the United States. A study of 1,599 older people found decreased markers of Alzheimer's pathology in the brain over a 30-year period.[122] This is almost certainly because of environmental factors: better education, medical care, living conditions, nutrition, control of hypertension and heart disease, and less smoking.[123] According to the US Census Bureau, among people aged 65 and older in 1965, only 5 percent had completed a bachelor's degree or more and, by 2018, this share had risen to 29 percent.[124] The observation that the risk of Alzheimer's disease is falling is strong support for the concept that preventive factors are important.

4. **Age does not need to limit our options.** Special problems may be encountered when encouraging older people to take preventive measures, as many older people and family members have rigid biases against the idea that they're capable of learning and of being physically active. A common view is that education applies only to the young. Many people also feel that if they are unable to run, they are unable to exercise. Furthermore, older persons often have less money than younger ones and have sensory deficits (visual, auditory, and vestibular), which impairs their opportunity to participate. They commonly have less access to transportation than the young. It is important to take these factors into account when planning lifestyle changes. Older persons can still exercise even if they can't

run. And alternate means of transportation may be needed for persons who can no longer drive.

Chapters 13 to 25 below provide a comprehensive discussion of lifestyle factors that may be considered in order to lower the risk of developing neurodegenerative disease, improve the body's resilience so that function can be maintained despite the development of disease, and enhance the capacity of the four reserve factors: cognitive, physical, psychological, and social. Enhancing these four reserve factors will enable you to augment your enjoyment of the opportunity that aging presents.

Enhancing these four reserve factors will enable you to augment your enjoyment of the opportunity that aging presents.

Changes in lifestyle behaviors, medications, and supplements should be discussed with a physician. I am not specific concerning the amount of exercise, dose of supplements, or targets for dietary consumption, because these figures will be highly variable from person to person and should be considered upon consultation with a physician.

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