

Editorial

A Modest Proposal for a Longitudinal Study of Dementia Prevention (with apologies to Jonathan Swift, 1729)

Robert P. Friedland* and Shivani Nandi

Department of Neurology, University of Louisville School of Medicine, Louisville, KY, USA

Accepted 13 August 2012

Abstract. Many studies have documented the role of risk and protective factors for late life dementing illnesses, particularly Alzheimer's disease. A "Systematic Review" from the US Agency for Healthcare Research and Quality and the National Institute on Aging concluded that because the overall quality of evidence was low, recommendations for public health could not be made. In order to gain evidence for the efficacy of lifestyle interventions, we propose a "Modest Proposal" to study 10,000 subjects over 40 years randomly assigned to groups of low or high saturated fat in the diet, head injury, and high or low levels of mental activity, physical activity, or inactivity as well as smoking or non-smoking. *This proposed study cannot be accomplished.* The "Modest Proposal" illustrates that the absence of definitive evidence should not restrict physicians from making reasonable recommendations based on the evidence that is available.

Keywords: Alzheimer's disease, dementia, epidemiology, prevention, risk factors

It has been widely proposed that dementia risk may be lowered through control of modifiable risk factors such as low levels of cognitive and physical activity, hypertension, obesity, high fat diet, head injury, diabetes mellitus, low dietary intake of fish, fruit and vegetables, antioxidants, B vitamins, and smoking [1, 2]. Yet, in a "Systematic Review" supported by the US Agency for Healthcare Research and Quality and the National Institute on Aging, Plassman and colleagues concluded, "few potentially beneficial factors were identified from the evidence on risk or protective factors associated with cognitive decline, but the overall quality of the evidence was low." The absence of randomized clinical trials was pointed out by the authors of the "Systematic Review" as a basis for this

conclusion. Therefore the authors concluded, "The current literature does not provide adequate evidence to make recommendations for interventions" [3, 4].

We agree that definitive evidence for the effectiveness of dementia prevention methods is lacking, and concur that large-scale population-based randomized clinical trials of these complex issues are critically needed. The NIH Conference Statement identified potential leads for dementia prevention, which they recommended should be pursued with "potentially novel approaches and increasingly rigorous scientific methods" [3]. We agree that current evidence to document the influence of lifestyle factors on cognitive impairment in late life are limited, and offer a "modest proposal" to obtain the needed evidence for the effectiveness of these interventions.

We propose a 40-year longitudinal single-blind study of these risk factors in 10,000 healthy volunteers, aged 20–30. Two thousand subjects each will be randomly assigned to groups of either high or low

*Correspondence to: Robert P. Friedland, MD, Department of Neurology, University of Louisville School of Medicine, 500 South Preston Street, Louisville, KY 40207, USA. Tel.: +1 502 852 2871; Fax: +1 502 852 6344; E-mail: robert.friedland@louisville.edu.

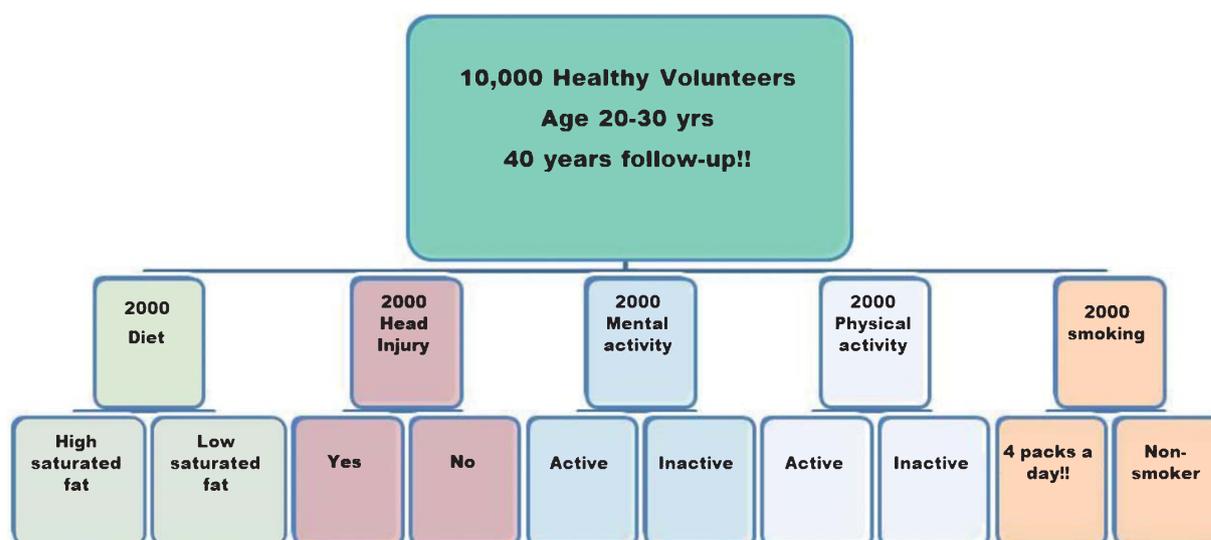


Fig. 1. Study Design. Two thousand healthy volunteers will be randomly assigned to 5 groups with mandated lifestyle interventions: high or low saturated fat diet, presence or absence of head injury, high or low levels of mental activity, high or low levels of physical activity, and 4 pack per day smoking or non-smoking. All of these 5 lifestyle factors will be maintained for 40 years and the effects of these interventions on the incidence and characteristics of dementia will be observed.

levels of intake of saturated fat, physical activity, cognitive activity, head injury or smoking (Fig. 1). The long period of observation is necessary because of the prolonged pre-clinical course of Alzheimer's disease (AD). The large number of subjects is required to allow for adequate statistical analysis considering the many covariates (age, gender, ethnicity, education, dropouts, and others). The importance of the results justifies the long period of observation and considerable expense.

But can such a study be done? It is time to realize that the ultimate study of the interactions of interest in regard to lifestyle and cognitive health in aging *cannot be done*. Yet the absence of definitive evidence should not restrict physicians from making reasonable recommendations based on the evidence that is available. For example, in an observational study, Johnson and associates studied the effects of blood pressure control on women with a 4.5 years follow up and concluded that "Hypertension and high blood pressure at baseline were not independently associated with MCI or probable dementia over time in older, cognitively intact, postmenopausal women..." [5]. This result does not inform as to whether a *lifetime* of blood pressure control will have a beneficial effect on cognitive outcomes in late life. There is ample evidence that midlife hypertension is associated with the risk of late life dementia [6]. Furthermore, a study of 8,534 Swedish twins found that obesity in midlife is a risk factor for dementia [7]. There is evidence to suggest that being overweight in

late life is not as much a risk factor for dementia as in midlife, because weight loss may occur with dementia onset [6]. While a randomized controlled trial of the effects of weight reduction over four decades of midlife cannot be performed, in the absence of conclusive evidence, it is clearly reasonable to advise avoidance of obesity in midlife as a dementia prevention method.

There are currently three dementia prevention trials underway in Europe. The "Prevention of Dementia by Intensive Vascular Care" study (ISRCTN29711771) examines the influence of control of vascular risk factors on the incidence of dementia or the burden of functional disability in the aged, with 3,700 subjects studied over 8 years. The "Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability" (NCT01041989) evaluates the effects of 2 years of interventions on cognitive impairment, dementia, and disability in 1,200 subjects. The "Omega-3 Fatty Acids and/or Multi-domain Intervention in the Prevention of Age-related Cognitive Decline" (NCT00672685) project examines the influence of isolated supplementation with omega-3 fatty acids on cognitive decline in 1,680 aged subjects, studied over nearly 6 years. We should keep in mind that even an eight-year study of these interventions will not tell us if early life interventions are effective. While the aforementioned European studies are an important step in the evaluation of potential interventions for dementia prevention [8], we do not need to wait for

their results to make reasonable recommendations for dementia prevention.

While most dementia intervention studies use older persons, a life-course approach is clearly preferable [9, 10]. Specifically, the most important time for the development of lifestyle factors influencing health is childhood [11]. Childhood is the most difficult period for research on these influences, because of the long period between childhood and the ages of risk, and the absence of informants who can tell us about the childhood of our aged research subjects. Public policy must take into account what we do know about dementia risk and work to enhance health-promoting behaviors in children, which have lifelong consequences. Several studies have shown the profound effects of education on dementia risk [12] and policies to enhance educational opportunities are clearly needed in our time of increasing longevity. The wisdom of these recommendations appears self-evident, yet the importance of education as a public health measure has not received sufficient emphasis. We cannot and must not wait until definitive proof on the value of such recommendations—such evidence will not be forthcoming.

Calculations of the population attributable risk of AD risk factors have led to the estimate that a 10–25% reduction in the main AD risk factors could potentially prevent as many as 1.1 to 3 million AD cases worldwide [2]. It is already well known that obesity, smoking, diabetes, hypertension, head injury, and low levels of education and mental and physical activity have negative effects on both systemic and brain health [13]. This message should be widely promoted, and there is every reason to promote healthy behaviors while continuing efforts to obtain further data.

In 1729 Jonathan Swift published anonymously “A Modest Proposal for Preventing the Children of Poor People in Ireland Being a Burden on Their Parents or Country, and for Making Them Beneficial to the Publick” [14]. He proposed that poverty in Ireland could be improved through the use of children for food. Our “Modest Proposal” is similarly intended as a satire, in order to emphasize the fallacy of assuming that because there are no randomized controlled trials we cannot make reasonable recommendations to lower dementia risk.

ACKNOWLEDGMENTS

This work was supported in part by the National Institutes of Health (AG017173).

Authors’ disclosures available online (<http://www.j-alz.com/disclosures/view.php?id=1493>).

REFERENCES

- [1] Middleton L, Yaffe K (2009) Promising strategies for the prevention of dementia. *Arch Neurol* **66**, 1210-1215.
- [2] Barnes DE, Yaffe K (2011) The projected effect of risk factor reduction on Alzheimer’s disease prevalence. *Lancet Neurol* **10**, 819-828.
- [3] Plassman BL, Williams JW Jr, Burke JR, Holsinger T, Benjamin S (2010) Systematic review: Factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med* **153**, 182-193.
- [4] Daviglus ML, Plassman BL, Pirzada A, Bell CC, Bowen PE, Burke JR, Connolly ES Jr, Dunbar-Jacob JM, Granieri EC, McGarry K, Patel D, Trevisan M, Williams JW Jr (2011) Risk factors and preventive interventions for Alzheimer disease: State of the science. *Arch Neurol* **68**, 1185-1190.
- [5] Johnson KC, Margolis KL, Espeland MA, Colenda CC, Fillit H, Manson JE, Masaki KH, Mouton CP, Prineas R, Robinson JG, Wassertheil-Smoller S, Women’s Health Initiative Memory Study, Women’s Health Initiative, Investigators (2008) A prospective study of the effect of hypertension and baseline blood pressure on cognitive decline and dementia in postmenopausal women: The Women’s health initiative memory study. *J Am Geriatr Soc* **56**, 1449-1458.
- [6] Qiu C (2012) Preventing Alzheimer’s disease by targeting vascular risk factors: Hope and gap. *J Alzheimers Dis*, in press.
- [7] Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L (2011) Midlife overweight and obesity increase late-life dementia risk: A population-based twin study. *Neurology* **76**, 1568-1574.
- [8] Richard E, Andrieu S, Solomon A, Mangialasche F, Ahtiluoto S, van Charante EP, Coley N, Fratiglioni L, Neely AS, Vellas B, van Gool WA, Kivipelto M (2012) Methodological challenges in designing dementia prevention trials - The European Dementia Prevention Initiative (EDPI). *J Neurol Sci*, (in press) doi:10.1016/j.jns.2012.06.012.
- [9] Qiu C, Kivipelto M, Fratiglioni L (2011) Preventing Alzheimer disease and cognitive decline. *Ann Intern Med* **154**, 212-213.
- [10] Brayne C (2007) The elephant in the room - healthy brains in later life, epidemiology and public health. *Nat Rev Neurosci* **8**, 233-239.
- [11] Friedland RP, Brayne C (2009) What should the pediatrician know about Alzheimer’s disease? *J Devel Behav Ped* **30**, 239-241.
- [12] Sharp ES, Gatz M (2011) Relationship between education and dementia: An updated systematic review. *Alz Dis Assoc Dis* **25**, 289-304.
- [13] Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Chen CH, Petot GJ, Debanne SM (2001) Patients with Alzheimer’s disease have reduced premorbid activities compared to healthy controls. *Proc Nat Acad Sci U S A* **98**, 3440-3445.
- [14] Swift, Jonathan (1729) A modest proposal for preventing the children of poor people of Ireland from being a burden to their parents or country, and for making them beneficial to the public. Published anonymously in Ireland.