Published in final edited form as:
Int Psychogeriatr. 2010 December ; 22(8): 1196–1202. doi:10.1017/S1041610210001080.

Prospects for delaying the rising tide of worldwide, late-life dementias

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Abstract

Worldwide, lifespan is lengthening. Concomitantly, late-life dementias are increasingly common, challenging both personal and public health internationally. After age 65, rates of dementia tend to double every five years in developed countries and every seven in developing ones. The late-life dementias, particularly Alzheimer's disease, have profound effects on aging individuals and their caregivers. Multidisciplinary research has explored the potential for various approaches to prevent or delay the onset of late-life dementias. Outlining that research, including our team's Adult Changes in Thought and Kame studies, this review concludes that delaying these dementias' onset appears feasible, although absolute prevention may not be. Today the most promising methods appear to include controlling vascular risk factors like hypertension and engaging in physical exercise—and possibly mental exercise—on and off the job. If people can delay the onset of dementias, they can lead more fulfilling lives for longer—spending less time suffering from dementia and letting their families spend less time coping with the disease. It is possible that trends toward more knowledge-based societies, where cognitive health is so vital, may increasingly exert evolutionary pressure favoring larger and healthier brains—and a "compression of cognitive morbidity"—well into old age. Public health's great triumph, increased lifespan, should give more of the world's people the reward of many years of dementia-free life—rather than the personal difficulties and public health burdens of many years of functional impairment, dependency, and suffering with dementia some interventions may delay the onset of Alzheimer's disease and other dementias.

Keywords

Alzheimer's disease; prevention; lifestyle risk factors; aging; exercise; demographics; evolution

Introduction

We are experiencing an international rising tide of late-life dementias. This rising tide is the result of the general lengthening of lifespan worldwide, which in turn stems from improvements in public health, education, and medical care. The increase in late-life dementias accompanying a longer lifespan poses serious challenges for both personal and public health in all the nations of the world (Larson and Langa, 2008).

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CONFLICT OF INTEREST DECLARATION: None

Dr. Larson delivered a version of this paper in September 2009 as a Plenary Presentation to the International Psychogeriatric Association in Montreal, Quebec, Canada.

Rates of dementia in the elderly have been found to vary widely among nations, but generally they are higher than had been thought previously (Llibre Rodriguez *et al.*, 2008). As a rule of thumb, after age 65, rates of dementia tend to double every five years in developed countries, and every seven years in developing ones (Lobo *et al.*, 2000). For people over age 85, the rate of dementia worldwide averages about 30 percent, with a dramatic increase after age 80 in developed nations (Graves *et al.*, 1996).

These dementias, particularly Alzheimer's disease and "mixed dementias" with more than one etiology (Langa *et al.*, 1994), have profound effects on aging individuals and their caregivers. It is no wonder that so much research is being devoted to exploring varied approaches to preventing or delaying dementias.

In this review, I outline the prospects for prevention of dementia, including Alzheimer's disease, with an emphasis on the role of lifestyle and vascular risk factors. The review is admittedly selective and emphasizes our own work, but I have included up-to-date reviews which generally confirm my ideas. I present descriptive evidence from survey data that rates of dementia in the United States may be decreasing. I discuss the possibility of a "compression of cognitive morbidity" as an achievable goal along with an evolutionary phenomenon related to society becoming more "knowledge based" in the 20th century (Drucker, 1983; Galbraith, 1967). And I emphasize the potential power of delaying the onset of dementia—if we make such efforts a priority in the increasingly aging societies of today and tomorrow. (Montine *et al.*, 2009).

Historical perspective

To understand how we got here, it is helpful to look backward. As recently as the early 1970s, experts considered cognitive decline, including extreme senility, to be part of the continuum of "normal aging;" and Alzheimer's disease was still lumped with Pick's disease as "pre-senile dementia." Since then, "senile dementia" has been recognized as largely due to Alzheimer's disease, indistinguishable from the classic form of the disease, which Alois Alzheimer first detected in a middle-aged patient.

In the 1970s and 1980s, research concentrated on distinguishing Alzheimer's disease from multi-infarct or vascular dementias. Since then, a dramatic increase in the prevalence of Alzheimer's disease and other dementias has been demonstrated in persons in their 80s and beyond. The dramatic increase is primarily explained by better detection and awareness of dementia in old age.

Research in the 1990s developed more precise definitions of Alzheimer's disease and its prevalence and pathologic features. In 1993, a seminal paper established that vascular dementia is more common in late life than had previously been realized (Skoog *et al.*, 1993). Mixed dementias became more commonly reported in clinical studies; and this was confirmed by reports of community-based neuropathologic studies (Lim *et al.*, 1999; Langa *et al.*, 1994).]

The past decade has seen research establishing that before age 65, dementias are rare; and after age 65, their incidence rises exponentially, with an even steeper up-sloping curve after 80 years of age (Graves *et al.*, 1996; Kukull *et al.*, 2002). In general, rates of dementia in higher-income countries somewhat exceed those in lower-income ones; however, rates are increasing around the world, particularly in urban Latin America and areas where overall longevity has improved (Llibre Rodriguez *et al.*, 2008).

Survival differences between people with dementia and without it become narrower the later their age at onset (Larson, Shadlen *et al.*, 2004). However, dementia is not inevitable, as

demonstrated by an individual living to ages as advanced as 115 years who showed no discernable neurodegenerative changes (den Dunnen *et al.*, 2008). Worldwide, reported rates of dementia vary widely.

As populations worldwide are increasingly aging, late-life dementias have far-reaching consequences for health. The rising tide of late-life dementia likely reflects gains in life expectancy. Dementia is likely made more evident as societies become increasingly "knowledge-based" (Drucker, 2001). Higher levels of education and the wealth generated by knowledge-based society are strongly associated with gains in life expectancy.

What influences the development of dementia?

Early-life socioeconomic status

Low socioeconomic status in early life is well known to affect growth and development, including that of the brain; and it has also been shown to affect the risks of other chronic diseases. The maturation of the brain continues into adolescence, and the areas that take the longest to mature—the intracortical association area and the hippocampal and reticular formations—are the same areas that show the earliest signs of Alzheimer's disease (Conel JL, 1967; Yakovlev and Lecours, 1967; Braak and Braak, 1991; Arriagada *et al.*, 1992). Therefore, it is no surprise that early-life characteristics associated with a lower socioeconomic environment tend to promote less healthy brain development and raise the risk of late-life Alzheimer's disease (Moceri *et al.*, 2000; Moceri *et al.*, 2001).

Moceri *et al.* used birth records on persons enrolled in the Group Health/ University of Washington Alzheimer Disease Patient Registry (ADPR) and the Genetic Differences Case-Control Study (Moceri, *et al.*, 2000) to relate early socioeconomic status to later dementia. We found results consistent with the hypothesis that a healthier socioeconomic environment in childhood and adolescence leads to more "brain reserve" (the brain's ability to cope with increasing age- and disease-related changes while still functioning) and less risk of late-life dementia, including Alzheimer's disease, later on. Factors associated with more favorable socioeconomic environments that appeared to protect against developing Alzheimer's disease included living in a suburb, having a father whose work was skilled and not manual, and having fewer siblings—with odds ratios of 0.45, 1.8, and 1.08 per added sibling, respectively. For people with the Apo (apolipoprotein) E4 allele, reared in the countryside, with several siblings and a father doing unskilled or manual work, the increase in risk was multiplicative. These findings are consistent with the brain reserve hypothesis. The influence of early "lifestyle" factors on the risk of Alzheimer's disease is noteworthy particularly for those persons at higher genetic risk of developing the disease, an example of a gene-environment interaction.

Education, occupation, and leisure activities

In general, evidence suggests that increasing education may have protective effects against developing dementia (Albert *et al.*, 2005; Schaie, 2005). This observation has a pathologic correlate: The dendritic field has been reported to be larger with increasing education levels (Gould *et al.*, 1999). This is also consistent with a link between education and brain reserve being preserved or enlarged.

The complexity of people's occupations also positively influences cognitive vitality, and this relationship becomes increasingly marked with age. Higher levels of cognitive function are also linked to an "engaged lifestyle," with leisure activities that are cognitively stimulating; of interest is that this association is stronger for blue-collar workers than for elite academics (Fratiglioni *et al.*, 2004)

Can a remedy prevent dementia?

The quest for a "fountain of youth," as old as Ponce de Leon, continues unabated. Long before dementia became an issue, "youth" was the focus of persons naturally yearning for a simple solution to aging. Now people seek a simple remedy to prevent Alzheimer's disease and other dementias. Ever since the late 1970s when Alzheimer's disease gained prominence, both scientists and laypersons have sought a golden pill to prevent or reduce the risk. In spite of claims and hopes, all of the simple preventive remedies have proven to be failures. Among the many examples of recent promising leads that resulted in dashed hopes are: antioxidant vitamins (Gray *et al.*, 2008); non-steroidal anti-inflammatory drugs (Breitner *et al.*, 2009); and ginkgo biloba (Snitz *et al.*, 2009). Likewise, cholinesterase inhibitors are also unlikely to provide a solution.

Many people have remarked that if only physical activity were a pill, it would be a popular medication indeed. Unlike the putative "magic bullets" listed above, physical activity, leisure activity, and social networks actually do seem promising as potential ways to help delay the onset of dementia. Their effects may be mediated by the plasticity of the brain, a phenomenon only recently realized.

Brain plasticity

Age-related declines in cognition and underlying brain function are not necessarily inevitable. It was long thought that damaged brain tissue could not regenerate or be restored. However, recent research suggests that lifestyle, education, occupation, expertise, and fitness can modify age-related declines in brain function, thanks to the plasticity of the brain (Kramer *et al.*, 2004). For instance, training in reasoning appeared to slow functional decline in Alzheimer's disease, with some cognitive abilities sustaining improvement for five years. (Willis *et al.*, 2006)

Physical activity, leisure activity, and social networks

In 2004, Fratiglioni *et al.* analyzed 13 published longitudinal studies relating dementia, including Alzheimer's disease, to social networks and leisure and physical activities (Fratiglioni *et al.*, 2004). All but one were conducted in Europe or North America; and all but one were embedded in large longitudinal population-based studies of aging starting with non-demented persons. Assessment was done at least three years after enrollment in 12 of the studies, and assessment ranged from one to seven years in the other study. Of the 13 studies, five focused on dementia, three on Alzheimer's disease only, and five on both Alzheimer's disease and dementia.

In seven of eight studies, physical activity—including exercise and daily physical activity—showed an inverse correlation to cognition. Beneficial effects of physical exercise have also been reported in diseases including hypertension, diabetes, obesity, osteoporosis, and depression. Questions of causation have been raised about the inverse correlation between physical activity and dementia and evidence that exercise might prevent dementia published at the time of this 2004 review was more equivocal. However, at least one study has suggested that poor physical function may precede the onset of dementia and Alzheimer's disease, with higher levels of physical function associated with a delayed onset. (Wang *et al.*, 2006).

The studies of non-physical leisure time activity mostly involved cognitively stimulating activity. In six of seven of these studies, leisure activity was inversely correlated with cognitive decline or lower cognitive performance. Other studies have linked leisure activity —attending cultural events, reading books or magazines, solving crossword puzzles, and

playing music or singing in a choir—with longer survival. This effect appears to be independent of the effect of fitness activity, which suggests involvement of mechanisms other than increased cardiopulmonary fitness.

The studies of social networks used disparate measures, but five of seven of them found the presence, quality, and size of a person's social network inversely related to the incidence of dementia. However, one concern about interpreting these findings is that declines in social network and physical and leisure activities—might represent a manifestation of early dementia rather than a pre-morbid risk factor: People may become less active physically and socially as a result of their experiencing cognitive decline.

Work from Fratiglioni's own group has suggested that physical, mental, and social components in leisure activities contribute equally to decrease the risk of dementia (Fratiglioni *et al.*, 2000; Karp *et al.*, 2006). Interesting and likely related recent research has suggested that maintaining a strong purpose for one's life may be protective against the development of Alzheimer's disease (Boyle *et al.*, 2010).

Growing evidence for vascular risk as a factor

Studies that rely on clinical criteria designed to detect Alzheimer's disease may not adequately discern vascular brain injury as the sole or concomitant cause of dementia. Evidence is growing that much dementia stems from vascular brain injury—from both small- and large-vessel disease, but especially the former. Vascular brain injury, Alzheimer's disease, and Lewy body disease occur through different disease processes to produce the phenotype of dementia. And the three processes can combine variably in individual patients to produce the dementia syndrome. For instance, neuropathologic studies have shown not only "plaques" and "tangles" (Braak stage) but microvascular infarcts account for risk of dementia (Sonnen *et al.*, 2007).

Growing evidence also suggests that limiting vascular risk can help delay late-life dementia. Since the 2004 review by Fratiglioni, *et al.*, the preponderance of evidence from observational and community-based studies and early trials strongly supports that among the vascular risk factors for dementia that can be modified, regular physical exercise has great promise. Descriptive studies including from our Adult Changes in Thought (ACT) project at Group Health have associated habitual exercise with significant reductions in the risks of both Alzheimer's disease and dementia from all causes (Abbott *et al.*, 2004; Larson *et al.*, 2006; Larson and Wang, 2004; Larson *et al.*, 2008; Podewils *et al.*, 2005; van Gelder *et al.*, 2004, Weuve *et al.*, 2004; Teri *et al.*, 2003). Our community –based descriptive cohort study found that compared with sedentary participants, exercise at least three times per week was associated with an approximate 40% reduction in dementia risk. Critical, systematic reviews of exercise and physical activity programs to improve cognitive function in old persons or for persons with dementia have shown some promise but have not been definitive (Angevaren *et al.*, 2008, Forbes *et al.*, 2008) because convincing evidence from randomized trials was not available.

In a recent well done randomized trial of exercise, Lautenschlager *et al.* (2008) showed that habitual physical exercise protected persons with subjective complaints about their memory ("mild cognitive impairment") from cognitive decline (Lautenschlager *et al.*, 2008). At the 18-month follow-up, this trial showed a statistically significant difference of 0.69 point between people who walked regularly and a sedentary control group in changes on the primary outcome measure, the Alzheimer Disease Assessment Scale–Cognitive Subscale scale. This "effect size" was greater than that for cholinesterase inhibitors (Malouf and Birks, 2004). This result is very important. Like the seminal randomized trial of Willis *et al.* (2006) showing proof of concept that reasoning training can ameliorate and even reverse age

related cognitive decline, we now have evidence from a clinical trial supporting a similar role for habitual physical exercise.

Other vascular risk factors are also of great interest. While randomized trials of antihypertensive drug treatments have not proved that treatment prevents dementia (McGuinness, Todd *et al.*, 2009), our research suggests an age varying association of high systolic blood pressure with incident dementia in young elderly persons (<75) but not in older subjects (Li, Rhew *et al.*, 2007). We also recently found that presence of cerebral microinfarcts was independently associated with high systolic blood pressure in younger participants (ages 65–80), especially those not taking antihypertensives (Wang *et al.*, 2009), but not in older participants. This suggests adequate antihypertensive treatment may reduce dementia risk by minimizing microvascular injury to the cerebrum.

The picture for cholesterol as a vascular risk factor and statins as modifiers may be similar. Earlier reviews have not concluded that treatment with statins had a beneficial effect on dementia risk (McGuiness, Craig, *et al.*, 2009). Descriptive studies have been plagued with methodologic inconsistencies and problems (Li *et al.*, 2004). In general, if there is an association with serum cholesterol and dementia risk it is likely restricted to mid and early late life cholesterol levels (possibly 15–20 years before onset), and not to late life levels (Li, *et al.*, 2005). In our neuropathology study of 110 subjects with brain autopsies ages 65–79 years and who were cognitively normal at enrollment in our Adult Changes in Thought study, findings demonstrated an association between antecedent statin use and reduced neurofibrillary tangle burden at autopsy. The risk for typical Alzhiemer's pathology was reduced in statin users, (OR 0.20; 95% Cl .05 – .86) (Li, Larson *et al.*, 2007).

Other vascular risk factors worth noting are smoking and diet. Although early reports emphasized that some nicotine exposure might be associated with reduced risk, more definitive research and reviews demonstrate smoking as a risk factor for cognitive decline and dementia (Anstey *et al.*, 2007). Recent research on diet include observations that a more Mediterranean diet and physical activity have been associated with reduced risk of Alzheimer's disease (Scarmeas *et al.*, 2009) and a more Mediterranean diet was associated with slower decline in mini-mental state examination (MMSE) (Féart *et al.*, 2009).

Clearly, vascular risk factors are of great interest for those interested in reducing late life risk of dementia and age-related decline. Exercise may turn out to be as close as we can come to the long-sought fountain of youth—and exercise, particularly walking—has no significant adverse effects. Control of other vascular risk factors like smoking, hypertension, adverse lipid pattern and diets, also show great promise especially in midlife and early old life before brain degeneration may become harder to reverse or prevent.

Trends and prospects

Recent trends in medical, lifestyle, demographic, and social factors have been positive for the cognitive health of older Americans—especially higher levels of education and better control of cardiovascular risk factors. Between 1982 and 2004, the National Long-Term Care Surveys showed significant decline in the prevalence of chronic disability, especially "mixed" dementia, among the Medicare-enrolled population in the United States (Manton *et al.*, 2005). The decrease was associated with higher levels of education and fewer cerebrovascular disease events. Data from the longitudinal U.S. Health and Retirement Study suggest decreasing rates of cognitive impairment in people over age 70: from 12.2% in 1993 to 8.7% in 2002. There was also a decrease in the interval between when substantial cognitive decline started and when death occurred. About 40% of the drop in the rates of cognitive decline were linked to higher education and wealth—and likely to improved control of cardiovascular risk as well (Langa *et al.*, 2008). Although this study has many

potential limitations, its findings suggest a "compression of cognitive morbidity," which is a desirable outcome: Fewer persons reach a threshold of significant cognitive impairment—and those who do have a more rapid decline to death (Fries, 1980). This compression was accidental—not planned—but it is of instructive value as we approach the rising tide of late-life dementias. Delaying the onset of dementia in even part of the at-risk population can decrease disease prevalence significantly, since patients are likely to die from another disease before dementia occurs (Brookmeyer *et al.*, 1998). If a one-year delay in onset could be achieved, it is estimated, it would prevent more than 9 million cases of Alzheimer's disease worldwide (Brookmeyer *et al.*, 2007).

Particularly in developed nations, society is now firmly knowledge based, and cognitive health is vital to successful development and especially maintaining high function and independence in late life. Rapid acquisition, use, and exchange of information—including Internet use—may have profound effects on brain development. For instance, recent selective evolutionary forces appear to favor the survival of three genes causing increased brain size and higher microglial density (Balter 2005, Evans *et al.*, 2005; Mekel-Bobrov *et al.*, 2005; Hayakawa *et al.*, 2005). Building our brains throughout life (through education and purposeful activity) and efforts to reduce neurodegenerative processes throughout life will likely have profound effects on individual and public health in this century of the brain.

Conclusion

Absolute prevention of late-life dementia is unlikely, especially as more people live longer. However, "compression of cognitive morbidity" is achievable, with dementia starting later and lasting for a shorter period. Better health and well-being throughout the lifespan, along with control of vascular risk, likely has benefited late-life risk. These trends and a growing evidence base supports further efforts to understand and ideally control vascular risk which appears to offer great prospects for preventing late-life dementias.

Acknowledgments

I thank and acknowledge excellent editorial work of Rebecca Hughes and Rita Weikal in developing this paper. I also thank the many staff and faculty who have worked on the Group Health/University of Washington Alzheimer's Disease Patient Registry (ADPR)/Adult Changes in Thought (ACT) study and on our community-based Kame project, an epidemiologic study of dementia in Japanese Americans in King County, Washington. Without their efforts since this work began in 1986, the material and ideas in this paper would not have existed. The projects were supported by grants from the National Institutes of Health, AG 06781 and AG 09769.

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