Title

Harnessing Brain Pathology for Dementia Prevention

Journal

JAMA Neurology, 81(3)

ISSN

2168-6149

Authors

Leng, Yue

Yaffe, Kristine

Publication Date

2024-02-05

DOI

10.1001/jamaneurol.2023.5490

Harnessing brain pathology in support of healthy lifestyle factors as strategies for dementia prevention

Yue Leng, PhD[1], Kristine Yaffe, MD[123]

1. *Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA;*
2. *Departments of Neurology and Epidemiology, University of California, San Francisco, CA;*
3. *San Francisco VA Health Care System, San Francisco, CA*

Alzheimer's disease (AD) and Related Dementia (ADRD) are devastating diseases that affect over 55 million people worldwide and imposes an estimated economic burden of over $800 billion annually[1]. This figure is projected to increase as the global population ages, with the prevalence of AD/ADRD expected to triple over the next 30 years[1]. To date, there is no cure to stop or reverse disease progression, underscoring the critical need for the development of primary or secondary prevention strategies that target modifiable risk factors to delay or prevent the onset of clinical symptoms.

Over the past decade, there has been ever-growing, yet controversial, evidence in the role of modifiable risk factors and risk reduction strategies for dementia. This is exemplified by the conflicting conclusions from two recent commissioned reports [2 3]. The National Academy of Medicine (NAM) report[2] concluded in 2017 that the evidence from large randomized controlled trials (RCTs), the ‘gold standard’ for evaluating an intervention’s effectiveness, is insufficient to support a public health campaign for dementia prevention. However, the report identified three intervention strategies with potential benefits: cognitive training, blood pressure management for people with hypertension, and physical activity. In contrast, the

2020 Lancet Commission report [3] advocated for a more ambitious and aggressive approach to prevention, based on evidence from both observational studies and RCTs, concluding that 40% of worldwide dementia cases could be prevented or delayed by modifying 12 risk factors: low education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution. While the discrepancies between these reports underscores the complexity of translating research evidence into both individual and policy recommendations, risk reduction interventions remain a promising, inexpensive and relatively safe strategy for lowering dementia risk.

In the current issue of JAMA Neurology, Dhana and colleagues[4] contribute important evidence to this debate by reporting a robust association between a composite healthy “lifestyle” score and cognitive function proximate to death, independent of AD/ADRD pathology burden~~, including β-amyloid load, phosphorylated tau tangle burden, and other dementia-related brain pathologies~~. The authors conclude that five lifestyle factors ~~(, including~~ diet, physical activity, cognitive engagement, smoking, and alcohol consumption~~),~~ may operate through both prevention and resilience in that cognitive benefits were observed even for those who had neurodegenerative pathologies. These interesting results add strengths to the concept that health and lifestyle factors are important strategies for prevention and suggest that several mechanisms may be at work.

A unique feature of the study by Dhana et al. is the comprehensive examination of brain pathologies of aging, including AD pathology, vascular disease-

~~(arteriolosclerosis and cerebral atherosclerosis)~~, Lewy Body disease, TDP-43, and hippocampal sclerosis, along with the longitudinal analysis of lifestyle score and cognition proximate to death among 586 decedents followed up to 24 years. A series of analyses showed that one point increase in the healthy lifestyle score (range 0 to 5, with higher score indicating a healthier lifestyle) was associated with 0.216 standardized units higher in cognitive performance (β=0.216; standard error (SE)=0.036; P-value<0.001), 0.120 units less β-amyloid load in the brain (β = -0.120; SE = 0.041; P-value = 0.003), and a higher healthy lifestyle score was associated with better cognition even after accounting for the combined burden of brain pathologies (β=0.166; SE=0.033; P-value<0.001).

While the observational nature of the study ~~limits the ability to infer~~makes it challenging to establish causality, it is an important step towards understanding the underlying mechanisms linking modifiable risk factors with AD/ADRD. Prior studies have found an association of increased brain amyloid load and tau aggregates with several modifiable risk factors [5–8], such as sleep disturbances, vascular risk factors (e.g., hypertension and diabetes), depression, and physical inactivity supporting a role for primary prevention. Others supported a potential “resilience” framework, where compensatory factors (e.g., high educational attainment, high cognitive and physical activity) appear to be protective of cognitive function even among those carrying high genetic risk for AD/ADRD or in the presence of AD pathologies[9]. Dhana et al.[4] demonstrated that only 11.6% of the effects of the lifestyle score on global cognition was through the pathway of β-amyloid load, while 88.4% was presumably a direct effect of lifestyle on cognition. Future studies are needed to clarify other

mechanisms that underlie the link between these risk factors and cognition ~~in late life~~.

In this study, Dhana et al.[4] computed averages of lifestyle scores from all available follow-up visits over a maximum of 2 decades. This approach helps reduce concerns about reporting bias and ~~One potential explanation is~~ "reverse causality", in ~~particularly~~ which ~~when~~ factors such as cognitive and physical activity are assessed in late life, close to clinical symptoms onset, might themselves be the consequence of prodromal changes in AD/ADRD that has been developing silently over the years. Over the past few years, ~~The need for~~t~~T~~here has been~~is~~ increasing recognition about a life course approach, which posits that risk factors operate over all life stages, to understand the causal nature and earliest effect of modifiable risk factors for dementia prevention ~~has gained increasing attention~~[2,3]. Emerging evidence suggests that cardiovascular risk factors, sleep fragmentation, and depression in early adulthood are associated with midlife cognition or risk of dementia[10–12], while mixed results have been found for physical activity, with studies showing evidence of reverse causation[13].

~~In this study, Dhana et al.[4] computed averages of lifestyle scores from all available follow-up visits over a maximum of 2 decades to mitigate measurement error due to self-reporting. While this helps to address the issue of reporting bias, reverse causation may still exist given that AD/ADRD pathology may take decades to develop and it is likely, although the information is not provided, that many did not have maximum follow-up time.~~ **Notably, participants in this study had a mean**

age at death of almost 91 years. Given that very old adults tend to have mixed brain pathologies and that many very old decedents are found to have incidental neuropathology, this could also explain why the association between lifestyle score, cognition and neuropathology was limited. This is supported by their age-stratified analysis in which the independent association between lifestyle and cognition was stronger for individuals who died at the age of 91 and older.

The use of a composite lifestyle score may be an accessible way to summarize and quantify the overall impact of lifestyle factors. However, it is not ~~it makes it difficult to determine, it fails to address potential colinear and~~ **possible** to investigate **interactive effects among different lifestyle factors** or~~, and~~ to identify which~~which~~. ~~Another important remaining question is which~~ **modifiable risk factors may confer the greatest benefits and should thus be prioritized in dementia intervention trials. Given that** ~~Dhana et al.[4] only included five risk factors,~~ **most of** the risk factors included in this study~~which~~ **have not previously associated with AD or vascular pathology,** ~~it is unsurprising that the relationship between the composite lifestyle score and cognition was mostly independent of dementia-related pathologies.~~ f~~F~~**uture research** might ~~should~~ **include other important risk factors better known to be linked with dementia-related pathologies, such as hypertension, diabetes, sleep disturbances, and depression[6,8]. Furthermore, since dementia is a complex condition that involves several risk factors and these in turn are often coexistent, there is growing recognition for a multidomain approach to dementia prevention, where both additive and synergistic effects between**

individual domains are considered. One of the first and largest multidomain RCTs, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial, suggested that a 2-year intervention targeting diet, exercise, cognitive training, and management of CVD risk factors improved global cognition modestly in older adults at high risk for dementia[14]. The U.S. trial, Protect Brain Health Through Lifestyle Intervention to reduce Risk (U.S. POINTER), has been launched to determine the effects of a FINGER-like multidomain intervention among older American adults[15]. More recently, exciting results from the Systematic Multi-Domain Alzheimer's Risk Reduction Trial (SMARRT), demonstrated that a 2-year personalized, multidomain risk reduction RCT improved cognition and risk factor profile among high-risk American older adults[16]. Each participant in the SMARRT intervention worked with a behavioral coach to develop a personalized plan related to their modifiable risk factors (from eight risk factors). Given these promising results, as well as the increasing number of modifiable risk factors that have been identified, future RCTs should be conducted targeting multiple modifiable risk factors, possibly earlier in the life course.

It has been over a decade since ~~we introduced~~ the concept of population attributable risk to project the public health impact of dementia risk factor reduction was introduced and found that 30-40% of dementia cases worldwide can be attributable to seven potentially modifiable risk factors[17]. Over the past decade, studies have identified an increasing

number of novel risk factors for dementia and have begun to uncover the mechanisms through which these modifiable risk factors could impact cognitive aging and prompted multidomain interventions. Despite this ongoing progress, critical questions remain to be addressed regarding the mechanistic pathways linking modifiable risk factors and cognitive aging and the directionality of this link. The study by Darhana et al.[4] is one of the first to harness brain pathology to investigate these mechanisms and ~~investigate these mechanisms~~ is a crucial step forward in addressing these important questions. -

There is an urgent need for more well-designed RCTs to pave the way for dementia risk reduction in the era of precision medicine. These strategies should be offered in conjunction with AD medications, similar to the approach in cardiovascular disease prevention and treatment in which medications along with lifestyle strategies are the standard of care.

References

1. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7(2):e105-e125. doi:10.1016/S2468-2667(21)00249-8
2. Leshner AI, Landis S, Stroud C, Downey A. *Preventing Cognitive Decline and Dementia: A Way Forward*. National Academy of Medicine; 2017.
3. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6/ATTACHMENT/DFC82F21-55AB-4950-8828-93F27077EF6D/MMC1.PDF
4. Dhana K, Agarwal P, James BD, et al. Healthy Lifestyle, Common Brain Pathologies, and Cognition in Community-Dwelling Older Adults. *JAMA Neurol*. Published online 2023.
5. Bubu OM, Pirraglia E, Andrade AG, et al. Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker changes. *Sleep*. 2019;42(6). doi:10.1093/SLEEP/ZSZ048
6. Winer JR, Deters KD, Kennedy G, et al. Association of Short and Long Sleep Duration With Amyloid-β Burden and Cognition in Aging. *JAMA Neurol*. 2021;78(10):1187-1196. doi:10.1001/JAMANEUROL.2021.2876
7. Rodriguez-Ayllon M, Solís-Urra P, Arroyo-Ávila C, et al. Physical activity and amyloid beta in middle-aged and older adults: A systematic review and meta-analysis. *J Sport Health Sci*. Published online August 7, 2023. doi:10.1016/J.JSHS.2023.08.001
8. van Arendonk J, Neitzel J, Steketee RME, et al. Diabetes and hypertension are related to amyloid-beta burden in the population-based Rotterdam Study. *Brain*. 2023;146(1):337-348. doi:10.1093/BRAIN/AWAC354
9. Casaletto KB, Staffaroni AM, Wolf A, et al. Active lifestyles moderate clinical outcomes in autosomal dominant frontotemporal degeneration. *Alzheimer's & Dementia*. 2020;16(1):91-105. doi:10.1002/ALZ.12001
10. Elser H, Horváth-Puhó E, Gradus JL, et al. Association of Early-, Middle-, and Late-Life Depression With Incident Dementia in a Danish Cohort. *JAMA Neurol*. 2023;80(9):949-958. doi:10.1001/JAMANEUROL.2023.2309
11. Yaffe K, Bahorik AL, Hoang TD, et al. Cardiovascular risk factors and accelerated cognitive decline in midlife. *Neurology*. 2020;95(7):e839-e846. doi:10.1212/WNL.0000000000010078
12. Leng Y, Knutson K, Carnethon MR, Yaffe K. Association between sleep quantity and quality in early adulthood with cognitive function in midlife. *Neurology*. 2023;in press.
13. Greendale GA, Han W, Huang MH, et al. Longitudinal Assessment of Physical Activity and Cognitive Outcomes Among Women at Midlife. *JAMA Netw Open*. 2021;4(3):e213227-e213227. doi:10.1001/JAMANETWORKOPEN.2021.3227
14. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus

control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *The Lancet*. 2015;385(9984):2255-2263. doi:10.1016/S0140-6736(15)60461-5

15. Baker LD, Snyder HM, Espeland MA, et al. Study design and methods: U.S. study to protect brain health through lifestyle intervention to reduce risk (U.S. POINTER). *Alzheimer's & Dementia*. Published online 2023. doi:10.1002/ALZ.13365

16. Yaffe K, Vittinghoff E, Dublin S, et al. Effect of Personalized Risk-Reduction Strategies on Cognition and Dementia Risk Profile Among Older Adults: The SMARRT Randomized Clinical Trial. *JAMA Intern Med*. Published online November 27, 2023. doi:10.1001/JAMAINTERNMED.2023.6279

17. Barnes DE, Yaffe K. The Projected Impact of Risk Factor Reduction on Alzheimer's Disease Prevalence. *Lancet neurology*. 2011;10(9):819. doi:10.1016/S1474-4422(11)70072-2