Original article

# Dementia prevention and reserve against neurodegenerative disease

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Similar to other complex disorders, the etiology of Alzheimer disease is multifactorial and characterized by an interplay of biological and environmental risk and protective factors. Potentially modifiable risk factors have emerged from epidemiological research and strategies to prevent neurodegeneration and dementia are currently being tested, including multimodal interventions aiming to reduce several risk factors at once. The concept of reserve was developed based on the observation that certain individual characteristics, such as life experiences, lifestyles, and neurobiological parameters, are associated with a higher resilience against neurodegeneration and its symptoms. Coordinated research is required to maximize the use of available human and financial resources to better understand the underlying neurobiological mechanisms of reserve and to translate research findings into effective public health interventions.



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## The challenges of aging societies

According to the World Health Organisation's (WHO) definition, healthy aging is "the process of developing and maintaining the functional ability that enables wellbeing in older age."[1] The new concept of decline of intrinsic capacities, comprising "the mental and physical capacities that a person can draw on [including] their ability to walk, think, see, hear, and remember," necessitates a repositioning of prevention efforts in the dementia space. The traditional definition of healthy aging as years lived free from disease is replaced by a concept focusing on a process that allows individuals to maintain their normal function as they age. This is in stark contrast to the usual health care and public health approaches, which mostly aim at identifying and treating acute illnesses rather than maintaining the intrinsic capacities throughout the life course. This paradigm shift in the definition of healthy aging will have to be followed by a process of redesigning the global health care systems with a stronger focus on preserving function for a longer period of time.

Treatment and prevention of dementia have long been considered impossible, but emerging evidence suggests that certain lifestyle choices are related to reduced risk, and that modification of lifestyle factors could be used to implement effective public health policies that promote healthy aging. A 2017 systematic review, commissioned by the US National Institutes on Aging, found that there is currently not enough evidence to justify large investments in public health initiatives geared to prevent dementia.[2] The report found a mix of negative and positive effects for differ-

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ent outcomes, with overall small effect sizes for several potentially preventive interventions, including physical activity, antihypertensives, non-steroidal anti-inflammatory drugs, vitamin B12, nutraceuticals, and multimodal interventions. Examples for large-scale dementia prevention programs with an approach that targets multiple interventional domains include the Multidomain Alzheimer Preventive Trial (MAPT),[3] the Prevention of Dementia by Intensive Vascular Care study (preDIVA),[4] the Healthy Ageing Through Internet Counselling in the Elderly study (HATICE)[5] and the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER).[6] Even though, for example, FINGER showed some positive cognitive effects of a 2-year trial which consists of exercise, dietary, and cognitive interventions in combination with vascular risk monitoring compared with general health advice, no such effects were found in the other studies. One explanation for these disappointing results is that the underlying biological mechanisms of risk and protective factors are still not well understood. The use of inappropriate end points is a major limitation of most studies, including insensitive cognitive tests, and biomarker surrogate endophenotypes my lead to better results, but current biomarkers do not seem to be suitable for this purpose.[7]

The terminology and definitions of Alzheimer disease (AD) and dementia are currently undergoing a transformation process, which is important to define disease categories based on biological evidence which can be targeted in treatment and prevention trials. However, constantly changing definitions make it difficult to compare studies and, at least in a transition period, make it more difficult to compare results. Also, there are different definitions of prevention and it is therefore crucial to agree on a commonly accepted terminology and aim to maximize the use of sparse research funding to conduct better studies. The total cost of developing an AD drug is estimated at over 5 billion USD, compared with less than 1 billion for cancer and the pharmaceutical industry average of under 3 billion.[8] The high costs and high failure rate associated with AD drug development has already resulted in some pharmaceutical companies focusing on more promising fields.

It is important to highlight that many of the described protective factors are interrelated

## Dementia prevalence and costs

The increase in life expectancy is one of the major achievements of modern societies. Global health care systems, however, are confronted with new challenges due to the constantly increasing number of older people. Age-associated chronic diseases are becoming more prevalent and lead to increased suffering for the affected individuals and their families and a higher financial burden for the communities. Dementia is among the most prevalent and therefore important chronic disorders in older people; most cases are related to AD pathology,[9] but other copathologies such as cerebrovascular lesions also play an important role and dementia is mostly caused by a mix of different pathologies in people over the age of 75 years.[10] According to estimates, 47 million people worldwide were affected by dementia in 2015 and this number is expected to double every 20 years (all things being equal). Therefore, 74 million people would be affected in 2030 and over 131 million in 2050.[11] In terms of the costs of dementia, over 1 trillion USD was spent in 2018 in the USA alone.[12] Only 15% of the costs is caused by medical care, the remaining 85% is related to social and family care. New health care models and public health approaches may replace at least some of the informal care, leading to reduced overall costs.

Even though dementia incidence and prevalence are on the rise globally, significant regional differences have been described, with a much stronger increase in low-income vs high-income countries. Currently about 58% of the global population live in low-income countries according to the WHO classification; this proportion is expected to increase to 63% in 2050,[13] which will contribute to the global burden of dementia cases. Reliable data show an increase in the age-associated incidence of dementia in lower income regions in Latin America, Asia, and Africa,[14] whereas the incidence are stable or decreasing in higher income regions, such as Europe and the USA.[15,16] Similar trend reversals are known from other areas of medicine, for example, cardiovascular disease, cancer, and diabetes mellitus, and are frequently related to improved prevention and treatment approach-

es.[13] It is important to point out though that the decreasing age-associated dementia incidence and prevalence in high-income countries does not equal a lower overall number of dementia cases, which is still increasing due to the higher average life expectancy.

## Risk and protective factors

The observation that the overall dementia risk is decreasing in Europe and other more developed countries leads to the important question about the underlying reasons.[17] Similarly to other complex diseases, the etiology of dementia is multifactorial and determined by complex gene-environment interactions. Genetic susceptibility is innate and nonmodifiable (except for epigenetic changes, which are related to environmental factors), but risk which is attributable to external parameters can potentially be modified and targeted by lifestyle intervention approaches aiming at preventing or slowing neurodegenerative changes (or its symptoms). Many of the currently known lifestyle-related risk factors of dementia are linked to factors such as vascular disease, obesity, and diabetes mellitus,[18] which all are potentially amenable to modification. In addition to risk factors, protective factors are increasingly receiving attention, including strategies to strengthen the reserve against neurodegenerative diseases, for example, by enhancing physical, social, and cognitive activities to enhance the resilience against dementia-related deterioration.[19]

A recently published expert consensus (The Lancet Commission on Dementia Prevention, Intervention, and Care)[20] suggests that about 35% of dementia can be explained by a set of nine risk factors in early, mid, and late life, including in descending order of importance, hearing loss, education to a maximum of age 11 to 12 years, smoking, late-life depression, physical inactivity, social isolation, midlife hypertension and diabetes mellitus, and midlife obesity. The magnitude of the overall dementia risk conferred by the identified, potentially modifiable risk factors is striking, in particular compared with the estimated 7% reduction in dementia incidence related to the complete elimination of the apolipoprotein E (APOE) ε4 allele, ie, the major genetic susceptibility factor for AD.[21]

The list of modifiable dementia risk factors indicates that relatively simple measures would potentially be effective dementia prevention tools. Better schooling, for example, is frequently associated with lower dementia risk and higher reserve against cognitive deterioration. It has also repeatedly been shown that better school education offsets the detrimental effects of brain damage (eg, due to neurodegenerative changes)[22]; this effect is not limited to AD, but has also been shown for other dementias such as frontotemporal dementia (FTD)[23,24] and dementia with Lewy bodies,[25] and other neurological and psychiatric disorders, including multiple sclerosis[26] and schizophrenia.[27] The concept of reserve was proposed to account for the repeated observation that individuals with certain characteristics have higher resilience against age- or disease-related brain changes.[28]

Schooling is used in many studies as a proxy measure of reserve because of its association with lower dementia risk and because it is a readily available outcome measure in clinical and epidemiological settings. School achievement is related to a diverse array of factors, which include genes, prenatal and early childhood development, socioeconomic and cultural parameters, and personality traits. There is also some conflicting evidence on the moderating effects of schooling on the lifetime rate of cognitive deterioration and some studies suggest that education in different life stages may have differential effects on sustained cognitive performance and reserve.[29] Since education is closely associated with the performance on the psychometric tests which are typically used to diagnose dementia, better performance may simply mirror formal education and not the degree of reserve against cerebral pathology.

Education (and related reserve proxies such as IQ or occupation) is influenced by characteristics of the environment.[30-32] For individuals with only limited access to formal education, other measures (such as literacy) may better correspond to their educational experiences.[33] In many Asian and African countries, for example, schooling is determined by socioeconomic variables (eg, the parent's income) rather than individual abilities and talents. Quality of education is another important aspect, which is not appropriately captured by a simple measure such as years of schooling.

The fact that formal education is typically completed by late childhood or early adulthood could suggest that

reserve is determined early in life and cannot be modified thereafter. However, several other mid- and late-life factors have also been identified, which appear to provide reserve against neurodegeneration. Working demands a large proportion of an adult's time and energy, and there is ample evidence that occupational attainment and certain job characteristics are associated with dementia risk. Intellectually demanding occupations, for example, appear to provide reserve against AD[34] and FTD,[35] similar to the musculoskeletal and vascular reserve provided by long-term physical activity. A large body of evidence confirms the link between occupation attributes and risk for cognitive deterioration and dementia,[36] and studies suggest that engagement in leisure and social activities[37] may also be protective concerning future deterioration. It is important to mention that the beneficial effects of active lifestyles are not limited to early and mid-life. Studies suggest that lifestyle changes in later life may also contribute to better cognitive outcomes.[38]

In addition to intellectual activities, there is evidence in support of the protective effects of noncognitive activities, suggesting that physically active individuals are at lower risk of cognitive deterioration[39] and dementia[40] compared with their less active counterparts. Biomarker studies indicate that the beneficial clinical effects of physical activity can also be demonstrated on a biological level, for example, by providing evidence in support of a hypothalamic-pituitary-adrenal axis response or cerebrospinal fluid AD marker changes in relation to aerobic exercise in individuals with mild cognitive deficits.[41,42] Interestingly, a decreased risk for cognitive decline has not only been shown for strenuous[43] but also for only moderate physical activitiy,[44,45] and it has been suggested that motor function per se has a reserve component too.[46]

## Genetic structure of reserve

Lifetime environmental exposures play an important role in determining the individual risk for cognitive decline and dementia, but nonenvironmental factors also have to be considered, including genetic and epigenetic parameters. Also, certain reserve-related factors are usually considered environmental, even though they are also influenced by genetic characteristics. For example, single nucleotide polymorphisms (SNP) have recently been discovered which are associated with education[47] and IQ.[48] Maximum adult head size, estimated by head circumference or intracranial volume is an important brain structural measure of reserve, which is associated with the perinatal environment,[49-51] but also with genetic variation.[52] Research on the genetic underpinnings of reserve has only recently been made possible by using genome-wide association studies (GWAS) to discover SNPs associated with risk and protective factors in increasingly large cohorts, required to be able to identify genetic variants with study-wide statistical significance. Large national resources such as the German National Cohort or UK Biobank will fuel further genetic research in the years to come.

GWAS have helped to discover important associations between reserve and dementia, including that dementia shares a substantial genetic basis with reserve.[53,54] Also, some of the shared SNPs appear to be related to effects already present in early life[55] or even in utero.[54] The importance of early-life development is underlined by studies showing a reduced risk of dementia and a smaller impact of neurodegeneration-related changes on cognitive performance in AD in individuals with larger vs smaller head size. Brain growth is largely complete by the age of six years and brain size is the main determinant of head size[56]; measures related to head size therefore reflect brain development early in life. An optimal brain growth therefore appears to be important for reserve against neurodegeneration and dementia decades later. Brain development is affected, in addition to genes, by external factors such as infections,[57] nutrition, and perinatal injury.[58] Large brains may simply contain more large neurons or synapses, but functional advantages may also play a role, such as better connectivity. But irrespective of the underlying mechanisms, early-life brain development seems to play a major role in providing reserve against age- and disease-associated brain changes; hence, public health measures to promote healthy brain growth are pivotal in terms of dementia prevention.

## Interventions for dementia prevention

It is important to highlight that many of the described protective factors are interrelated. For instance, education and other environmental factors strongly influence literacy, and intelligence has a strong effect on school

achievements.[59] The level of schooling is associated with occupational attainment, but occupations are also a form of lifelong education. Socioeconomic factors in general are also relevant determinants of education, occupation, leisure, and social activities. Individuals with protective lifestyles are less likely to drink alcohol and smoke and are more likely to be physically active and have better diets. Genetic factors also seem to (co) determine many behavioral choices such as daily physical activity,[60] smoking,[61,62] and eating habits.[63] This underlines that studying reserve-related factors in isolation may not be the appropriate approach. Studies need to adopt a more inclusive strategy, taking into consideration that epidemiological risk and protective factors may represent interrelated constructs to a certain degree.

These considerations emphasize the need for life course research to capture a multitude of variables from birth and onward. For lifestyle interventions aimed at improved dementia prevention, multimodal approaches may be more appropriate than strategies only targeting a single candidate lifestyle factor. The development of effective lifestyle-modifying interventions is methodically challenging because of the slowly progressive nature of most late-onset neurodegenerative diseases, including AD, with a clinically silent stage over many years (or even decades) before the first symptoms appear. Therefore, studies either have to run over many years, limiting their feasibility, or surrogate markers have to be used to measure effectiveness, such as imaging or other biological measures. So far, using surrogate endophenotypes as primary outcomes has not been successfully implemented in prevention trials, but some encouraging results have still been reported.

The first nonpharmacological intervention trials emerged in the early 2000s. Most of them concentrated on a single modality, for example, testing the effects of aerobic exercise, cognitive training, or nutritional counselling on relevant outcomes such as vascular disease. Overall, results were mixed, and the field developed towards conducting multidomain interventions, combining the individual interventional strategies which had previously been developed and investigated. The initial findings from these more recent dementia prevention studies indicate that multidomain interventions may offer certain benefits in older individuals at risk for cognitive decline.[5,64]

At the same time, findings from individual studies have not been consistently replicated so far in independent cohorts, and some trials show no effects of multidomain approaches.[65,66] Also, it is questionable whether the same interventions can be expected to affect different disorders, for example AD and FTD. The existing data also does not allow differentiating between neuroprotective and symptomatic effects of the interventions. More biologically rooted concepts are therefore needed. However, irrespective of the exact mechanisms, even small symptomatic effects may suffice on a population level to result in a meaningful reduction of dementia cases.[67]

## Conclusions

Dementia risk is determined by a complicated interplay of factors (both environmental and genetic), some of which are modifiable and amenable to lifestyle interventions. The dementia field is currently undergoing a major paradigm shift towards more biologically oriented definitions and disease concepts (such as the 2018 National Institute on Aging – Alzheimer's Association research framework)[68] and clinical trial design, including nonpharmacological trials, will have to adapt to these changes. The urgent desire to develop more effective, ie, disease-modifying, drugs is the main driver for the conceptual changes; however, some recent trials were able to show significant positive effects on secondary biomarker study end points, while at the same time failing to show clinically meaningful effects on cognition or daily function.[69] Those studies emphasize that identifying relevant pathophysiological targets is important, but showing clinically meaningful benefits for affected or at risk of dementia populations is even more important. The same notion applies to both pharmacological and nonpharmacological strategies.

There is sufficient evidence to substantiate that AD-type pathology is the most prevalent cause of dementia in older individuals. At the same time, studies also suggest that the association between AD pathophysiological changes and cognitive performance is attenuated in the oldest-old.[70] This suggests that other pathologies may play an increasingly important role as people are getting older, and the strict categorization of dementia subtypes based on the underlying pathological changes is called into question. On the one hand, a substantial proportion of

seemingly "pure" AD cases have mixed pathologies at autopsy (cerebrovascular lesions in many cases); on the other hand, AD-typical Aβ plaques are frequently found in cognitively intact older individuals.[71]

Epidemiological studies highlight the importance of lifestyle-related and environmental protective and risk factors. It may be particularly important to try to improve unhealthy lifestyles during midlife, with a focus on vascular health.[72] Improved education, reduced vascular burden and other positive, for example societal, changes during the last 20 to 30 years have probably led to a decreasing dementia risk. However, this claim only holds true for high income countries,[17,73] while dementia incidence and prevalence are on the rise in poorer countries,[14] further increasing the economic burden and inequality between the developed and developing world. To design and implement more effective dementia prevention strategies and programs, which also involve low income regions, the fragmented population-based research landscape has to be aligned more closely. Research should account for the differences between global regions (for example concerning the educational systems) and relevant associations between dementia risk factors on different levels (biological, societal, psychological) have to be studied more closely. Research should also cross the traditional boundaries between the disciplines and disease entities, for example, applying similar approaches to study AD and other dementias or unrelated neurological and psychiatric disorders.

Apparently, close collaboration between groups and comparison and contrasting of data and results will be required to develop more effective treatment and prevention options. Due to the high heterogeneity of human environmental and genetic data, harmonized approaches which help reduce unwanted variation and noise are required to make progress. The pooling of data and open access to the relevant resources is also key to motivate more researchers globally to work together, including those who do not have the financial resources or infrastructure to establish their own cohorts. Databases such as the International Alzheimer's and Related Dementias Research Portfolio (https://iadrp.nia.nih.gov/about), which aims to collect and categorize information about the major funding organizations' portfolios, are helpful in streamlining funding strategies and maximizing resources to increase the positive impact of research on public health and to avoid duplication of activities. Such efforts, however, will need to be proceeded by the establishment of appropriate ethical, legal, and social rules and agreements accepted across regional boundaries, as advocated by the World Dementia Council, for instance (https://worlddementiacouncil.org/our-work). ■

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## References

**1.** *WHO Clinical Consortium on Healthy Ageing 2017 – report of consortium meeting 21 and 22 November 2017 in Geneva, Switzerland.* Geneva:2018.
**2.** Kane R, Butler M, Fink H, et al. *Interventions To Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia. Comparative Effectiveness Review No. 188.* [Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2015-00008-I]. AHRQ Publication No. 17-EHC008-EF. Rockville, MD:2017.
**3.** Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol.* 2017;16(5):377-389.
**4.** Moll van Charante EP, Richard E, Eurelings LS, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet.* 2016;388(10046):797-805.
**5.** 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. *Lancet.* 2015;385(9984):2255-2263.
**6.** Barbera M, Mangialasche F, Jongstra S, et al. Designing an internet-based multidomain intervention for the prevention of cardiovascular disease and cognitive impairment in older adults: the HATICE Trial. *J Alzheimers Dis.* 2018;62(2):649-663.
**7.** Kemppainen N, Johansson J, Teuho J, et al. Brain amyloid load and its associations with cognition and vascular risk factors in FINGER Study. *Neurology.* 2018;90(3):e206-e213.
**8.** Cummings J, Reiber C, Kumar P. The price of progress: Funding and financing Alzheimer's disease drug development. *Alzheimers Dement (N Y).* 2018;4:330-343.
**9.** Scheltens P, Blennow K, Breteler MM, et al. Alzheimer's disease. *Lancet.* 2016;388(10043):505-517.
**10.** Korczyn AD. Mixed dementia - the most common cause of dementia. *Ann N Y Acad Sci.* 2002;977:129-134.
**11.** *World Alzheimer report - the global impact of dementia.* Alzheimer's Disease International, London; 2015.
**12.** Wimo A, Guerchet M, Ali GC, et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement.* 2017;13(1):1-7.
**13.** Cea-Soriano L, Fowkes FGR, Johansson S, Allum AM, Garcia Rodriguez LA. Time trends in peripheral artery disease incidence, preva-

lence and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK. *BMJ Open.* 2018;8(1):e018184.
**14.** Chan KY, Wang W, Wu JJ, et al. Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: a systematic review and analysis. *Lancet.* 2013;381(9882): 2016-2023.
**15.** Matthews FE, Stephan BC, Robinson L, et al. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. *Nat Commun.* 2016;7:11398.
**16.** Wimo A, Sjolund BM, Skoldunger A, et al. Cohort effects in the prevalence and survival of people with dementia in a rural area in northern Sweden. *J Alzheimers Dis.* 2016;50(2):387-396.
**17.** Matthews FE, Arthur A, Barnes LE, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet.* 2013;382(9902):1405-1412.
**18.** Baumgart M, Snyder H, Carrillo M, Fazio S, Kim H, H J. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers Dement.* 2015;11(6):718-726.
**19.** Perneczky R, Alexopoulos P, Schmid G, et al. [Cognitive reserve and its relevance for the prevention and diagnosis of dementia]. *Nervenarzt.* 2011;82(3):325-330, 332-335.
**20.** Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet.* 2017;390(10113):2673-2734.
**21.** Ritchie K, Carriere I, Ritchie CW, Berr C, Artero S, Ancelin ML. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. *BMJ.* 2010;341:c3885.
**22.** Perneczky R, Drzezga A, Diehl-Schmid J, et al. Schooling mediates brain reserve in Alzheimer's disease: findings of fluoro-deoxy-glucose-positron emission tomography. *J Neurol Neurosurg Psychiatry.* 2006;77(9):1060-1063.
**23.** Perneczky R, Diehl-Schmid J, Drzezga A, Kurz A. Brain reserve capacity in frontotemporal dementia: a voxel-based 18F-FDG PET study. *Eur J Nucl Med Mol Imaging.* 2007;34(7): 1082-1087.
**24.** Perneczky R, Diehl-Schmid J, Pohl C, Drzezga A, Kurz A. Non-fluent progressive aphasia: cerebral metabolic patterns and brain reserve. *Brain Res.* 2007;1133(1):178-185.
**25.** Perneczky R, Haussermann P, Diehl-Schmid J, et al. Metabolic correlates of brain reserve in dementia with Lewy bodies: an FDG PET study. *Dement Geriatr Cogn Disord.* 2007;23(6): 416-422.
**26.** Rimkus CM, Avolio IMB, Miotto EC, et al. The protective effects of high-education levels on cognition in different stages of multiple sclerosis. *Mult Scler Relat Disord.* 2018;22:41-48.
**27.** Amoretti S, Cabrera B, Torrent C, et al. Cognitive reserve as an outcome predictor: first-episode affective versus non-affective psychosis. *Acta Psychiatr Scand.* 2018;138(5):441-455.
**28.** Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol.* 2012; 11(11):1006-1012.
**29.** Zahodne LB, Stern Y, Manly JJ. Differing effects of education on cognitive decline in diverse elders with low versus high educational attainment. *Neuropsychology.* 2015;29(4):649-657.
**30.** Duncan GJ, Brooks-Gunn J, Klebanov PK. Economic deprivation and early childhood development. *Child Dev.* 1994;65(2 Spec No):296-318.
**31.** Sacker A, Schoon I, Bartley M. Social inequality in educational achievement and psychosocial adjustment throughout childhood: magnitude and mechanisms. *Soc Sci Med.* 2002; 55(5):863-880.
**32.** McKeown T, Record RG. Relationship between childhood infections and measured intelligence. *Br J Prev Soc Med.* 1976;30(2):101-106.
**33.** Manly JJ, Touradji P, Tang MX, Stern Y. Literacy and memory decline among ethnically diverse elders. *J Clin Exp Neuropsychol.* 2003; 25(5):680-690.
**34.** Karp A, Andel R, Parker MG, Wang HX, Winblad B, Fratiglioni L. Mentally stimulating activities at work during midlife and dementia risk after age 75: follow-up study from the Kungsholmen Project. *Am J Geriatr Psychiatry.* 2009;17(3):227-236.
**35.** Spreng RN, Drzezga A, Diehl-Schmid J, Kurz A, Levine B, Perneczky R. Relationship between occupation attributes and brain metabolism in frontotemporal dementia. *Neuropsychologia.* 2011;49(13):3699-3703.
**36.** Qiu C, Karp A, von Strauss E, Winblad B, Fratiglioni L, Bellander T. Lifetime principal occupation and risk of Alzheimer's disease in the Kungsholmen project. *Am J Ind Med.* 2003; 43(2):204-211.
**37.** Bennett DA, Arnold SE, Valenzuela MJ, Brayne C, Schneider JA. Cognitive and social lifestyle: links with neuropathology and cognition in late life. *Acta Neuropathol.* 2014;127(1):137-150.
**38.** Wang HX, MacDonald SW, Dekhtyar S, Fratiglioni L. Association of lifelong exposure to cognitive reserve-enhancing factors with dementia risk: A community-based cohort study. *PLoS Med.* 2017;14(3):e1002251.
**39.** Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med.* 2011;269(1):107-117.
**40.** Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology.* 2001;57(12):2236-2242.
**41.** Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol.* 2010;67(1):71-79.
**42.** Baker LD, Bayer-Carter JL, Skinner J, et al. High-intensity physical activity modulates diet effects on cerebrospinal amyloid-beta levels in normal aging and mild cognitive impairment. *J Alzheimers Dis.* 2012;28(1):137-146.
**43.** Albert MS, Jones K, Savage CR, et al. Predictors of cognitive change in older persons: MacArthur studies of successful aging. *Psychol Aging.* 1995;10(4):578-589.
**44.** Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. *Arch Intern Med.* 2001;161(14): 1703-1708.
**45.** Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology.* 1995;45(6):1161-1168.
**46.** Elbaz A, Vicente-Vytopilova P, Tavernier B, et al. Motor function in the elderly: evidence for the reserve hypothesis. *Neurology.* 2013; 81(5):417-426.
**47.** Okbay A, Beauchamp JP, Fontana MA, et al. Genome-wide association study identifies 74 loci associated with educational attainment. *Nature.* 2016;533(7604):539-542.
**48.** Savage JE, Jansen PR, Stringer S, et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet.* 2018;50(7): 912-919.
**49.** Guo LH, Alexopoulos P, Wagenpfeil S, Kurz A, Perneczky R, Alzheimer's Disease Neuroimaging I. Brain size and the compensation of Alzheimer's disease symptoms: a longitudinal cohort study. *Alzheimers Dement.* 2013; 9(5):580-586.
**50.** Perneczky R, Alexopoulos P, Wagenpfeil S, Bickel H, Kurz A. Head circumference, apolipoprotein E genotype and cognition in the Bavarian School Sisters Study. *Eur Psychiatry.* 2012;27(3):219-222.
**51.** Perneczky R, Wagenpfeil S, Lunetta KL, et al. Head circumference, atrophy, and cognition: implications for brain reserve in Alzheimer disease. *Neurology.* 2010;75(2):137-142.
**52.** Adams HH, Hibar DP, Chouraki V, et al. Novel genetic loci underlying human intracranial volume identified through genome-wide association. *Nat Neurosci.* 2016;19(12):1569-1582.
**53.** Brainstorm C, Anttila V, Bulik-Sullivan B, et al. Analysis of shared heritability in common disorders of the brain. *Science.* 2018;360(6395).
**54.** Ikram MA, Fornage M, Smith AV, et al. Common variants at 6q22 and 17q21 are associated with intracranial volume. *Nat Genet.* 2012;44(5):539-544.
**55.** Dean DC, 3rd, Jerskey BA, Chen K, et al. Brain differences in infants at differential genetic risk for late-onset Alzheimer disease: a cross-sectional imaging study. *JAMA Neurol.* 2014;71(1):11-22.

**56.** Sinclair D. *Human Growth after Birth.* Oxford: Oxford University Press; 1998.
**57.** Hagberg H, Mallard C. Effect of inflammation on central nervous system development and vulnerability. *Curr Opin Neurol.* 2005; 18(2):117-123.
**58.** Tan MJ, Cooke RW. Improving head growth in very preterm infants--a randomised controlled trial I: neonatal outcomes. *Arch Dis Child Fetal Neonatal Ed.* 2008;93(5):F337-341.
**59.** Richards M, Sacker A. Lifetime antecedents of cognitive reserve. *J Clin Exp Neuropsychol.* 2003;25(5):614-624.
**60.** Beunen G, Thomis M. Genetic determinants of sports participation and daily physical activity. *Int J Obes Relat Metab Disord.* 1999;23 Suppl 3:S55-63.
**61.** Koopmans JR, Slutske WS, Heath AC, Neale MC, Boomsma DI. The genetics of smoking initiation and quantity smoked in Dutch adolescent and young adult twins. *Behav Genet.* 1999;29(6):383-393.
**62.** Madden PA, Heath AC, Pedersen NL, Kaprio J, Koskenvuo MJ, Martin NG. The genetics of smoking persistence in men and women: a multicultural study. *Behav Genet.* 1999;29(6):423-431.
**63.** van den Bree MB, Eaves LJ, Dwyer JT. Genetic and environmental influences on eating patterns of twins aged >/=50 y. *Am J Clin Nutr.* 1999;70(4):456-465.
**64.** Chhetri JK, de Souto Barreto P, Cantet C, et al. Effects of a 3-year multi-domain intervention with or without omega-3 supplementation on cognitive functions in older subjects with increased CAIDE dementia scores. *J Alzheimers Dis.* 2018;64(1):71-78.
**65.** van Middelaar T, Hoevenaar-Blom MP, van Gool WA, et al. Modifiable dementia risk score to study heterogeneity in treatment effect of a dementia prevention trial: a post hoc analysis in the preDIVA trial using the LIBRA index. *Alzheimers Res Ther.* 2018;10(1):62.
**66.** Soininen H, Solomon A, Visser PJ, et al. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. *Lancet Neurol.* 2017;16(12):965-975.
**67.** *World Alzheimer report - dementia and risk reduction.* London, UK: Alzheimer's Disease International; 2014.
**68.** Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018;14(4):535-562.
**69.** Rinne JO, Brooks DJ, Rossor MN, et al. 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. *Lancet Neurol.* 2010;9(4):363-372.
**70.** Imhof A, Kovari E, von Gunten A, et al. Morphological substrates of cognitive decline in nonagenarians and centenarians: a new paradigm? *J Neurol Sci.* 2007;257(1-2):72-79.
**71.** Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med.* 2011;1(1):a006189.
**72.** Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci.* 2009;11(2):111-128.
**73.** Qiu C, von Strauss E, Backman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. *Neurology.* 2013;80(20):1888-1894.