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Life-course epidemiology in dementia - state of the art

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Dementia is defined as a clinical syndrome characterized by progressive deterioration in multiple cognitive domains that are severe enough to interfere with daily functioning. It was estimated that worldwide more than 25 million people were affected by dementia in 2005, with 5 million new cases occurring every year (1). Dementia is a principal cause of functional dependence, institutionalization, and death in older people. Since the 1980s, numerous community-based studies focusing on aging and health in elderly people have been launched in the world. These studies, joined by several long-term observational studies that were initially focused on cardiovascular disease of middle-aged people, have significantly contributed to the understanding of etiology of dementia and thus, pave the way for potential intervention.

Life-course perspective in dementia risk

Dementia is a multifactorial disorder. The risk of late-life dementia is determined by exposures experienced over the lifespan. The pathways of different risk factors leading to dementia are not fully understood, but several etiological hypotheses have been proposed such as vascular hypothesis, inflammatory hypothesis, oxidative-stress hypothesis, and toxic exposures (**Fig 1**) (2). These hypotheses highlight potential links of various risk factors to brain pathologies that may cause the dementia syndrome. For instance, both vascular and neurodegenerative pathways may play a part in the association of high homocysteine with brain aging and dementia; inflammatory markers are likely to reflect both peripheral and cerebrovascular mechanisms that may be linked to dementia. Furthermore, epidemiological research has also suggested that psychosocial and healthy lifestyle factors may postpone the onset of dementia, possibly by enhancing cognitive reserve. These factors include high

education and socioeconomic status (SES) in early-life as well as rich social network, social engagement, mentally-stimulating activity, and regular physical exercise over adult-life. In addition, several follow-up studies have reported a decreased risk of dementia associated with healthy dietary patterns and nutritional factors such as high adherence to a Mediterranean diet as well as dietary or supplementary intake of antioxidants (e.g., vitamins E and C) and ω-3 polyunsaturated fatty acid.

Systematic reviews and meta-analyses have highlighted the relevance of a life-course perspective in studying the risk and protective factors for dementia because this approach has helped to demonstrate that age or specific time-windows of exposures as well as accumulative or combined exposures are critical in determining the risk of late-life dementia (2,3). This life-course approach in dementia has been supported by numerous reports, such as:

1. Longitudinal studies often report a decreased incidence of dementia, and of Alzheimer's disease (AD) in particular, associated with high SES and educational achievement early in life.
2. Long-term observational studies of the general population have consistently suggested that elevated blood pressure in midlife, especially when not controlled with antihypertensive agents, is associated with an increased risk of dementia in late-life.
3. Similarly, several studies also showed that possessing a few other vascular risk factors in midlife such as obesity and high total cholesterol was more consistently associated with an increased risk of late-life dementia. For example, the HARMONY study of dementia among Swedish twins suggested that being obese at midlife was associated with a nearly 4-fold increased odds ratio of dementia. However, epidemiological evidence supporting a risk effect of having these vascular risk factors in late-life (e.g., 75+ years) in dementia is less evident, indicating the relevance of the time at exposure in the dementing disorder.

4. Diabetes in association with dementia is supported by systematic reviews and meta-analyses of longitudinal studies, which show that diabetes is associated with an approximately 2-fold increased risk of dementia (3). Furthermore, in the Kungsholmen Project, borderline diabetes or impaired glucose regulation was associated with an increased risk of dementia and AD independent of future development of diabetes, possibly by accelerating the progression of mild cognitive impairment to dementia (4). Borderline diabetes may also interact with severe systolic hypertension to synergistically increase the dementia risk. Long-term observational studies show that midlife-onset diabetes as compared to late-life diabetes is more strongly associated with an elevated risk of dementia, even when controlling for the duration of diabetes (5)

In conclusion, the life-course model for dementia risk is now well recognized by the scientific community. This model has several implications. Most importantly, any preventive or therapeutic intervention programs targeting, for example, vascular risk factors are likely to be effective only if implemented from midlife. Other implications are discussed below.

Cumulative and combined exposures

The combined or cumulative effect of multiple risk factors on the risk of dementia has been investigated in several population studies. For example, the large-scale community-based Faenza Project in Italy detected a joint effect of age, stroke, and education on the odds of dementia, such that older people as compared to younger persons had a higher prevalence of dementia across various educational and stroke groups. Furthermore, stroke is a strong risk factor for dementia among younger-old and highly educated subjects; the onset of dementia might occur about 10 years earlier owing to stroke, possibly by accelerating progression from cognitive impairment no dementia to clinical dementia. Other explicative examples derive

from the Swedish Kungsholmen Project, the Finnish CAIDE data, and a few other population-based studies, which consistently suggested a cumulative effect of aggregating vascular disorders on dementia risk such that an increasing burden of multiple vascular risk factors and disorders was associated with an increased risk of the dementing disorder.

The combined effect of genetic-environmental or environmental-environmental joint exposures may lead also to the attenuation of the dementia risk. For example, in the CAIDE study, more frequent leisure-time physical activity in midlife was associated with a reduced risk of dementia; such effect was particularly strong among carriers of the APOE ε4 allele, suggesting that physical activity may modify the effect of the ε4 allele on the risk of dementia. Furthermore, the Kungsholmen data also suggested that work complexity with data and people was related to a decreased risk of dementia and that the highest level of work complexity may modulate the increased dementia risk due to low education.

Increased dementia risk with advanced age

Both prevalence and incidence of dementia increase steeply with advancing age. Globally, the prevalence of dementia was estimated to be approximately 3.9% in people age 60+, with prevalence varying from 1.6% to 6.4% by regions across the world. In Europe, the pooling data of population surveys suggest that the age-standardized prevalence of dementia in people aged 65+ years is 6.4%. The prevalence of dementia doubles almost every 5 years from 65 years until very old ages; nearly half of the oldest-old people (90+ years) become demented. Thus, the overall prevalence and the burden of dementia depend largely on age structure of the population. Similar to prevalence, the incidence of dementia increases substantially with age. The pooling data of population-based incidence studies in Europe suggested that approximately 2 per 1000 person-years become demented in people aged 65-69 years, and the

incidence increases to 70-80 per 1000 person-years for people 90+ years (6). Therefore, as population ages, the number of patients with dementia is projected to nearly double every 20 years (1).

Mixed dementia

The strong association of dementia with age leads to the fact that in the general population 70% of the dementia cases are over age 75 (6). At these advanced ages, more than 50% of people are affected by multimorbidity as defined by the presence of two or more chronic conditions (7). As comorbidity is a common feature among patients with dementia (8), it is plausible to hypothesise that different pathologies may affect also the brain. Using current clinical criteria, we are used to state that AD and vascular dementia (VaD), the two main dementia subtypes, account for approximately 70% and 20%, respectively, of all dementia cases. In the Kungsholmen Project of 75+ years old people, over 50% of AD cases had vascular involvements, suggesting that patients with “pure” AD and “pure” VaD constitute only a minority of all dementia cases. These clinical observations are supported by neuropathological and neuroimaging data, which show that there is a spectrum of dementia-associated brain pathologies from relatively pure vascular pathologies on one end and relatively pure Alzheimer pathologies on the other end, and in-between the majority of dementia cases are likely owing to cerebrovascular and neurodegenerative pathologies (9). Therefore, in most cases, clinical dementia represents a mixture of neurodegenerative and cerebrovascular pathologies that may be impossible to untangle, especially among very old people. If these observations question the traditional classification scheme of AD and VaD, from the public health perspective, the ultimate purpose becomes to prevent the dementia syndrome as a whole.

Conclusions

In summary, dementia will reach an epidemic level in the coming decades as a result of population aging and the lack of effective intervention strategies. This will pose a serious threat to public health as well as to the social and economic development of the modern society. Research from multidisciplinary perspectives involving such as epidemiology, neuropathology, and neuroimaging has provided sufficient evidence that vascular risk factors significantly contribute to the expression and progression of cognitive aging including dementia, whereas active engagement in social, physical, and mentally-stimulating activities may delay the onset of the dementia syndrome. A promising strategy to deal with dementia is to implement intervention programs that take into account both the life-course perspective and the multifactorial nature of the disease. The multi-domain interventions should include strategies to enhance cognitive reserve as well as maintaining vascular health by adopting actively-integrated lifestyles and optimally controlling vascular disorders to reduce the burden of vascular lesions in the brain. These intervention studies need to have sufficient sample size and several branches to be able to further clarify which interventions can better help people to maintain their cognitive ability as long as possible or at least to delay the dementia onset.

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Fig. 1. Etiological hypotheses for dementia from life-course perspective