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Review article

Risk factors of cognitive impairment: Impact of decline in oral function☆

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ABSTRACT

Cognitive impairment and subsequent dementia are the major causes of disability and need for nursing care among older people in worldwide. The purpose is to review well-known risk factors for cognitive impairment and dementia, focusing on the relationship between decline in oral function and current prevention strategies. Various non-modifiable and modifiable risk factors are related to cognitive impairment. Effects of oral function to cognitive impairment is not yet well recognized in the medical community, although masticatory function, occlusal force, and number of teeth have been reported to be related to cognitive function. Furthermore, occlusal force rather than number of teeth was significantly related to the early stages of cognitive impairment, and that a decline in occlusal force seemed to lead to cognitive impairment directly and indirectly through dietary intake. This relationship was significant only for occlusal force, which may be associated with the early stages of cognitive decline. Nutritional change caused by reduced masticatory function is suggested as a possible explanation. Therefore, rehabilitation or maintenance of oral function should be sought to prevent cognitive impairment.

Contents

1. Introduction

The proportion of old-old people has dramatically increased during the past two decades, accelerated by a decrease in the birth rate. The proportion of the old-old population (over 75 years) in Japan was only 1.3 % of the entire population in 1950, but it rapidly rose from the 1990s and reached 15 %, the highest rate in the world, in 2020 [1]. Among old-old populations, increased demand for nursing care has become a major problem in terms of increasing costs and personnel burdens. In Japan, the demand for nursing care for old people has been increasing every year, and the number of old people requiring nursing care is more than 6.5 million, which is 5 % of the total population and 18 % of the old population. Recent figures show that in males and females aged from 70 to 74 years, only 5 % need nursing care. However, these rates increase markedly in people over the age of 85 years, of whom one-third of males and half of

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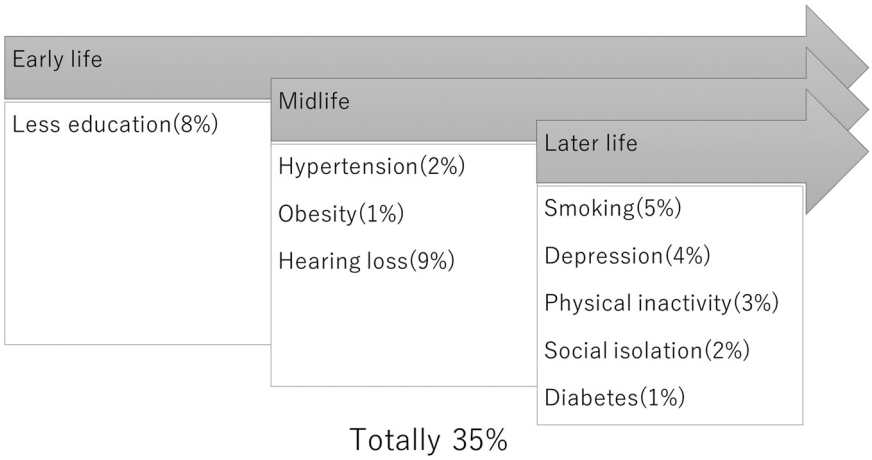

Fig. 1. Modifiable dementia risks in various stages in life [5]. A total of 35 % potentially modifiable dementia risk factors affect each stage of life.

females need nursing care [2]. These statistics may not be unique to Japan and will be common around the world in the near future.

Dementia is the top reason for patients to require nursing care in Japan [3]. According to a World Health Organization report [4], dementia is a syndrome in which there is deterioration in memory, thinking, behavior, and ability to perform everyday activities. It has a physical, psychological, social, and economic impact, not only on people with dementia, but also on their carers, families, and society. The number of people with dementia was 50 million in 2015 and is projected to reach 78 million in 2030, and 139 million in 2050. There are many different forms of dementia and Alzheimer's disease (AD) is the most common form and may contribute to 60–70 % of cases. Other major forms include vascular dementia, dementia with Lewy bodies, and a group of diseases that contribute to frontotemporal dementia. The signs and symptoms linked to dementia can be understood in three stages as following; forgetfulness, losing track of the time and becoming lost in familiar places in the early stage, becoming forgetful of recent events and people's names, becoming confused while at home, having increasing difficulty with communication, needing help with personal care and experiencing behavior changes, including wandering and repeated questioning in middle stage and becoming unaware of the time and place, having difficulty recognizing relatives and friends, having an increasing need for assisted self-care, having difficulty walking and experiencing behavior changes that may escalate and include aggression in late stage.

Livingston et al. reported that 65 % of dementia was due to non-modifiable factors and 35 % was due to modifiable factors [5] (Fig. 1). Non-genetic, modifiable risk factors play important roles and could be a focus for interventions to reduce disease risk or delay disease onset. One report [6] discusses various factors, such as genetic, socioeconomic, life-related and nutritional factors, that can be considered as modifiable risk factors for dementia. In a recent review [5], the following nine modifiable risk factors were listed: depression, hypertension, hearing impairment, less education, smoking, obesity, diabetes, physical inactivity, and low social contact. And three more factors were added in 2020 [7]: air pollution, excessive alcohol consumption, and traumatic brain injury. These factors account for around 40 % of worldwide dementia, which therefore could theoretically be prevented or delayed. Mild cognitive impairment (MCI) is defined as an objective cognitive impairment and is considered to be the state between health and early dementia. Mitchell et al. [8] reported that about 39 % of people diagnosed with MCI developed dementia in the subsequent 10 years.

In recent years, many longitudinal studies have investigated the relationship between oral health and cognitive function [9–11]. Cerutti-Kopplin et al. [12] concluded in their systematic review that individuals with suboptimal dentition (less than 20 teeth) faced a 20 % higher risk of developing cognitive decline and dementia than those with optimal dentition after adjusting for other risk factors. The risk factors for cognitive impairment have increased in number year by year, but oral health and oral function have never been recognized as major risk factors. The relationship between oral factors, such as number of teeth, occlusal force, and masticatory function, and cognitive impairment has recently been recognized, and a decline in oral function should be considered as a new risk factor.

Prevention or delayed onset of dementia is a matter of the highest urgency in an aging society. It is therefore important to prevent patients from falling into cognitive impairment, which is a precursor of dementia. This review aims to provide a brief description of current knowledge about the risk factors for cognitive impairment and subsequent dementia, to mention about the relationship between decline in oral function and cognitive impairment, and to consider prevention strategies to reduce or delay the onset of dementia.

2. Risk factors for dementia

2.1. Non-modifiable factors

Genetic factors, such as the genes of *apolipoprotein E (ApoE)ε4*, amyloid precursor protein, and presenilin 1 and 2 (PSEN1 and PSEN2), are reported to be representative of the onset of dementia [13]. In particular, the *ApoEε4* allele is well known as the main risk factor for late-onset AD. However, the other three genes are involved in the pathogenesis of early-onset dementia.

Age and sex are also known to be unmodifiable factors. Older age is the highest risk factor for dementia and the incidence increases sharply over the age of 65 years. One study reported that 80% of people with dementia were over 75 years old [14]. It is also reported that while age on its own is less powerful than other risk factors, it remains an important consideration [5]. Sex differences feature as factors in the progression and onset of dementia, and being female was recognized as a risk factor for non-amnestic MCI in some meta-analyses and reviews [15–17]. Several reasons, such as a longer lifetime exposure to estrogens [18] and the decline in estrogen in adulthood [19], have been suggested to explain the higher risk in females, but no obvious reason has emerged. Estrogen reduction during menopause may be a key factor.

Protein markers have been found in the cerebrospinal fluid or peripheral blood specifically related to neutrophil activity in patients with AD or MCI [20]. In particular, an increased concentration of an

abnormal cerebrospinal fluid tau-protein has been reported to be a significant predictor of dementia and MCI [21].

2.2. Modifiable factors

Several factors can contribute to increase dementia risk at various stages in life. For example, education is an important factor in early life (aged younger than 45 years); hypertension, obesity and hearing loss are important factors in midlife (aged from 45 to 64 years); and smoking, depression, and physical inactivity are important factors in later life (aged older than 65 years) [5,7]. Representative factors are described briefly below.

Lower educational level in early life has been regarded as a risk factor for dementia. Wei et al. reported in their meta-analysis that the dementia risk was reduced by 7 % for each additional year of education [22]. However, another meta-analysis found that a high education level had no major association with the progression to AD in patients with MCI [23]. The difference seemed to be caused by the cut-off point between high and low educational levels. A low education level is thought to result in vulnerability to cognitive decline.

Cardiovascular and metabolic diseases in midlife, such as hypertension, diabetes, high cholesterol, and obesity, were also reported in many studies as risk factors for dementia [5,7,13]. Vascular risk factors were reported to lead to dysfunction in the blood-brain barrier and a reduction in cerebral blood flow [24], causing neuronal damage. High cholesterol and diabetes, especially type 2 diabetes, were reportedly associated with dementia via several mechanisms, including resistance, deficient or impaired insulin receptors, and vascular inflammation [25]. The mechanism by which obesity and higher body mass index are related to the development of AD is still unknown and controversial. In fact, some researchers found that low weight was also a risk factor for AD [26] and that obesity in later life was inversely correlated with the risk of dementia [27]. However, most of the current reviews and longitudinal studies conclude that obesity and a body mass index over 30 kg/m^2 in midlife are risk factors [28].

Smoking has also been implicated as a cause of cognitive impairment in past studies, with suggested mechanisms including an increase in free radicals and oxidative stress, promotion of pro-inflammatory action, and activation of phagocytes [13]. Additionally, smoking is a risk factor for cerebrovascular disease [29], which is itself a risk factor for dementia; thus, smoking affects dementia both directly and indirectly.

Other important risk factors are psychosocial factors, and social and physical inactivity. Symptoms of depression can be part of the clinical presentation of dementia, and the risk of dementia is increased by the effect of depression on stress hormones, neuronal growth factors, and hippocampal volumes [30]. Social isolation is a prodrome of dementia and results in cognitive inactivity and subsequent acceleration of cognitive decline. Social isolation also affects other risk factors of dementia, such as hypertension and depression [31]. Depression and social and physical inactivity seem to affect each other, resulting in a negative effect on dementia and cognitive impairment.

Because many nutrients are associated with brain health, nutrient intake and dietary patterns may also affect cognitive function [5,7,13,32]. It has been increasingly reported that poor nutrient intake is negatively associated with cognitive function [33]. High levels of saturated and trans fats are known to be a risk factor for cardiovascular disease; they also affect brain blood vessels and contribute to cognitive impairment [34]. Fructose may have a negative effect on cognitive function by affecting phosphorylation of insulin receptors, which leads to brain insulin resistance and memory impairment [35]. Other nutrient factors, such as excessive iron and copper intake and synthetic folate or folic acid with a low vitamin B12 status have been reported as risk factors [36].

3. Oral health and cognitive impairment/dementia

A systematic review about the association between the number of teeth and incidence of dementia initially yielded 419 articles [37]. Finally, 11 cohort studies were selected to investigate the relationship between the number of remaining teeth and the development of dementia in later life. The meta-analysis revealed that the group of subjects with a high number of residual teeth was associated with a decreased risk of dementia of approximately 50 % (pooled odds ratio = 0.483; $p < 0.001$). In a narrative review about the relationship between oral health and cognitive impairment [38], a decline in masticatory function, mainly caused by tooth loss, was shown to affect cognitive function through various mechanisms. In the other review of 16 reports about the relationship between oral health and dementia [39], two points were suggested. One is poor oral hygiene is associated with dementia, and more so amongst people in advanced stages of the disease. And the other is suboptimal oral health, such as gingivitis, dental caries, tooth loss, and edentulousness, appears to be associated with increased risk of developing cognitive impairment and dementia. In recent meta-analysis about the relationship between periodontal disease and cognitive disorder, risk of cognitive decline in increased with periodontal disease severity [40]. The other meta-analysis [12] showed that there are three possible mechanisms by which tooth loss leads to cognitive decline: tooth loss may reduce sensory stimulation to the brain, dental status can be linked to cognitive impairment via the nutritional pathway, and periodontal disease may play a role through neuro-inflammation. According to these meta-analyses, periodontal disease was discussed previously their relation to cognitive impairment, and tooth loss was thought to be outcome of periodontal disease rather than a risk factor in itself.

Tooth loss is associated with poor masticatory function and it may affect stimulation of the central nervous system [41]. Some animal studies showed the relationship between masticatory function and cognitive impairment. Various mechanisms about this relationship were shown; for example, reduced masticatory function causes an impairment of the cholinergic neurotransmitter system associated with learning ability and spatial memory or reduced neurogenesis of the brain. About the influence on brain, Furukawa et al. reported the possibility that decreased occlusal support in mice affect cognitive function and activity by neural activity and neuroinflammation in the hippocampus and hypothalamus [42], and Oue et al. reported that tooth loss caused astrogliosis in the brain of mice [43]. Gobel proposed a mechanism by which decreased mastication-induced sensory stimulation leading to degeneration of secondary neurons in the spatial pathway of the alveolar and trigeminal nerves and through downstream cortical-brainstem circuits, contribute to diminished cortical cholinergic function [44]. There are also reports that edentulous mice induce hippocampal neural cell loss, alters astroglial behavior in the hippocampus [45], and changes hippocampal gene expression [46]. In human study, Winning reported that tooth loss was associated with regional reduced gray matter volume in the brain [47].

The effects of mastication on the brain have also been reported in terms of its association with cerebral blood flow. Hotta et al. reported that their experiments using rats revealed that the nucleus basalis of Meynert associated with masticatory motor commands was more activated during chewing, suggesting its involvement in the relationship between chewing and higher brain functions [48]. Furthermore, Hasegawa et al. measured jaw movements and cerebral blood flow in humans, suggesting that the brain's autoregulation is well-maintained during jaw movement [49,50]. Miyake et al. also reported that chewing exercise can promote adequate blood supply to the brain, potentially contributing to the prevention of Alzheimer's disease [51]. In the systematic review about mastication and cognitive decline [52], the brain areas most activated during

mastication were the frontotemporal cortex, caudate nucleus, and thalamus, revealing a positive correlation between chewing intensity and blood flow in the principal trigeminal nucleus. The increase in cerebral blood flow was measured through a local vasodilator effect, resulting in increased neuronal metabolism in the region associated with learning and memory. And this review concluded that masticatory function has the potential to act as a protective factor in patients with cognitive impairments and neurodegenerative diseases, and increased cerebral blood flow has been suggested as a mechanism underlying this effect. These reports suggest the possibility of a direct mechanism in which mastication-induced jaw movements increase cerebral blood flow to the brain and activate higher brain functions.

Reduced masticatory function also affects dietary intake [53]. People with poor masticatory function may tend to avoid eating food high in essential micronutrients and fiber and eat food high in cholesterol and saturated fats [41]. Diet can explain associations between oral health and dementia or cardiovascular disease. Takeshita et al. [54] reported about the relationship between oral function and cognitive function based on the results of their cohort study. The number of teeth, occlusal force, and mean periodontal pocket depth were significantly related to cognitive function. But periodontal status and the number of teeth were not significantly associated with cognitive function after adjusting for occlusal force. This result suggested that occlusal force, number of teeth, and periodontal status are mutually correlated, and occlusal force may be the most important oral factor (Table 1).

The report about nutritional intake [55] indicated that people with lower occlusal force tended to avoid vegetables and fruits, and therefore habitually received significantly less vitamins A, C, E, and B and dietary fiber, which play an important role in protecting against cellular damage and chronic diseases such as cancer and cardiovascular disease. Another study investigating occlusal force, cognitive function, and nutritional intake [56] found that the intake of green and yellow vegetables bore a positive significant relationship to the cognitive function score. To examine the direct and indirect effects of occlusal force on cognitive function, a path analysis using structural equation modeling was conducted from the results of the above studies (Fig. 2). The path model revealed that cognitive function is directly associated with age, micro-inflammation, depression, dietary intake, educational level, and occlusal force, and occlusal force was associated with cognitive function, both directly and also indirectly through dietary intake. Jockusch et al. investigated the differences in chewing function and related parameters by stratified the participants into groups depending on the degree of dementia, and only maximal occlusal force showed significantly difference among the groups [57]. As already mentioned, dietary intake is associated with cognitive impairment and other systemic diseases associated with cognitive impairment. Therefore, occlusal force must be an important factor for cognitive function.

Table 1
Correlation between cognitive function and possible risk factors.

Variables	rs	*p*-value
Sex (female)	0.094	0.003
Education level	0.343	< 0.001
Financial status	0.146	< 0.001
Smoking	-0.100	0.003
Drinking	-0.119	< 0.001
Hypertension	-0.094	0.003
BMI	-0.098	0.002
Depression score	-0.096	0.003
High sensitive CRP (inflammation)	-0.133	< 0.001
Dental status		
Number of teeth	0.133	0.002
Occlusal force	0.186	< 0.001
Mean PPD (mm)	-0.022	0.492
Percentage of PPD ≥ 4 mm teeth (%)	-0.044	0.190

rs: Spearman's rank correlation coefficient.
BMI: body mass index.
CRP: C-reactive protein.
PPD: periodontal pocket depth.
Education level, financial status, drinking, and CRP were significantly correlated with cognitive function. In dental status, only occlusal force was significantly correlated.

The results of 3-year longitudinal study [58] revealed that 25 % of participants with posterior occlusal support (remaining teeth) had reduced cognitive function, compared with 37 % of participants without posterior occlusal support. Furthermore, the participants with lower occlusal force recorded a faster pace of cognitive decline over time after controlling for possible confounders [59]. Other significant predictors for cognitive decline were male gender, older age, less education, higher C-reactive protein level, lower hand-grip strength, slower walking speed, and lower economic status. Number of teeth and occlusal force were associated with cognitive function even after adjusting for other risk factors. Furthermore, maintaining more teeth and a stronger occlusal force buffered cognitive decline.

In contrast, there are reports showing that masticatory function is not related to the risk of dementia. Dintica et al. reported in their longitudinal study [60] that poorer posterior support is associated with age-related decline in spatial/fluid ability. However, they did not find that poorer masticatory function was associated with a higher risk of dementia. Their finding was in line with another study [61] that investigated the relationship between masticatory function and dementia. In recent review about the relationship between mastication and cognition in human, a cause-effect relationship has not been proven [62]. Furthermore, one critical opinion proposed that people with better childhood cognitive function have better oral health, and those with less function experience higher disease rates, resulting in greater incremental tooth loss [63]. While some reports have shown that tooth loss, occlusal force, and masticatory function are associated with cognitive decline, others have shown that they are not.

4. Prevention of dementia

There are many possible protective factors for dementia and cognitive impairment when considering the abovementioned risk factors. According to a recent review [7], the following preventive strategies are recommended. In terms of reducing neuropathological damage, such as amyloid, tau-mediated and vascular or inflammatory damage, it is recommended to minimize diabetes, treat hypertension, prevent head injuries, stop smoking, reduce exposure to air pollution, and reduce midlife obesity. In terms of increasing or maintaining cognitive reserve, it is recommended to treat hearing impairment, maintain frequent social contact, and attain a high level of education. Cognitive reserve is the concept that people who have such a brain reserve can tolerate more neuropathology without cognitive and functional decline; this is related to either the brain's anatomical substrate or the adaptability of cognition. Maintaining frequent exercise, reducing the occurrence of depression, and avoiding excessive alcohol intake are reported to be effective in both of these aspects. Nutritional intake or dietary pattern was also reported as a preventive factor in many reviews. Green and yellow vegetables and fruits (sources of folate, vitamin E, and carotenoids), seafoods (sources of n-3 fatty acids) and berries (sources of polyphenols) have positive associations with cognition according to some reviews [32]. Monounsaturated fats, carotenoids, and vitamin D are also effective in reducing cognitive decline, although available data is limited. The Mediterranean diet [32,33], which requires daily intake of fish, olive oil, and potatoes, moderate wine consumption, and restricted intake of sodium, saturated fat, and sweets is attracting attention as the diet with the most positive relationship to the prevention of cognitive decline.

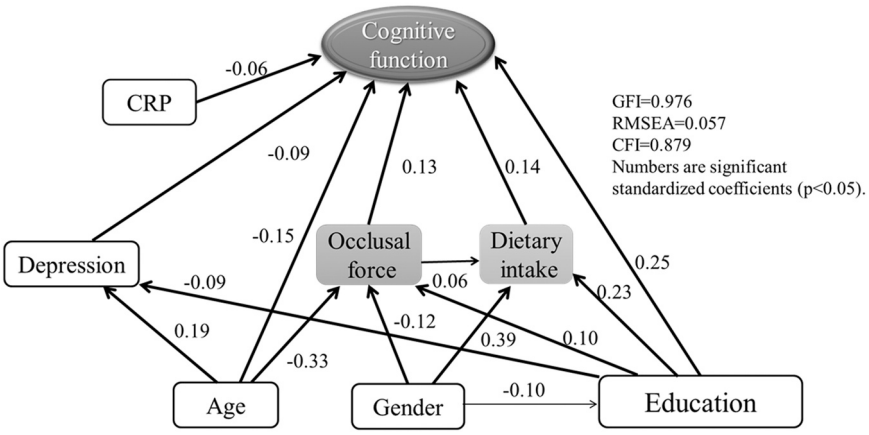

Fig. 2. Path analysis from occlusal force to cognitive function [56]. Cognitive function was directly associated with age, CRP, depression, dietary intake, educational level, and occlusal force. The occlusal force was associated with cognitive function, both directly and also indirectly through dietary intake.

In terms of nutritional intake and oral function, maintaining oral health by preventing tooth loss and decrease of occlusal force and maintaining healthy periodontal tissue helps maintain good nutritional intake and a balanced diet. The results of these studies about oral function and cognitive decline highlight the value not only of abovementioned oral rehabilitation but also of oral maintenance, such as practicing regular oral hygiene and attending dental checkups, in delaying cognitive decline and preventing dementia, which in turn can delay cognitive decline and prevent dementia.

5. Conclusion

1. Various factors have already been reported as risk factors for cognitive impairment or dementia and further risk factors are still emerging. However, oral function is not yet regarded as a major risk factor in the medical community.
2. Masticatory function may be associated with the early stages of cognitive decline. Changes in nutrition induced by reduced masticatory function, which is caused by tooth loss and a decline in occlusal force, is suggested as a possible explanation.
3. A controlling study analyzing possible confounders including socioeconomic status and medical condition shows that occlusal force is significantly related to cognitive function rather than the number of teeth.

Conflicts of interest

None.

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