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Analysis of Risk Factors for Cognitive Frailty: A Meta-Analysis

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A B S T R A C T

Background: Cognitive frailty (CF) is a syndrome characterized by cognitive and physical decline in older adults, which increases the risk of disability, dependency, and mortality. This study aims to identify and analyze risk factors for CF incidence through a systematic review and meta-analysis. **Methods:** A literature search was conducted on PubMed, Scopus, and Web of Science databases until June 2024. Observational studies reporting associations between potential risk factors and CF incidence in the elderly population were included. Two independent researchers performed study selection, data extraction, and risk of bias assessment. Meta-analysis was performed using a random effects model, and heterogeneity between studies was evaluated. **Results:** A total of 25 studies (n=45,678 participants) met inclusion criteria. Meta-analysis showed that advanced age (OR=1.89; 95% CI 1.65-2.16), female gender (OR=1.38; 95% CI 1.19-1.60), history of cardiovascular disease (OR=1.52; 95% CI 1.23-1.87), diabetes mellitus (OR=1.45; 95% CI 1.18-1.78), depression (OR=2.08; 95% CI 1.72-2.51), and low physical activity (OR=1.63; 95% CI 1.35-1.97) are risk factors significant for the incidence of CF. Low educational level (OR=1.71; 95% CI 1.43-2.04), low socioeconomic status (OR=1.58; 95% CI 1.29-1.93), and smoking history (OR=1.31; 95% CI 1.05-1.64) were also associated. with an increased risk of CF. **Conclusion:** This study identified several modifiable and nonmodifiable risk factors for CF occurrence. Interventions targeting these risk factors may help prevent or delay the development of CF in older adults.

1. Introduction

Cognitive frailty (CF) is a relatively new concept but is increasingly important in the field of geriatrics and public health. CF refers to a condition in which an individual experiences a concomitant decline in cognitive and physical function, but does not meet the diagnostic criteria for dementia or severe disability. This condition is often considered a transitional stage between healthy aging and dementia and has been shown to be associated with an increased risk of various health problems, including disability, dependency, frailty, and even death. Although there is no universal consensus on the definition of CF, most experts agree that CF includes two main components: cognitive decline, which can take the form of impaired memory, attention, or executive function, as well as physical decline, which can take the form of muscle weakness, decreased walking speed, or decreased overall physical activity. These cognitive and physical declines are not only interrelated, but can also exacerbate each other, creating a vicious cycle that can accelerate overall health decline. The prevalence of CF varies depending on the population and criteria used but is estimated to range from 7% to 25% in seniors aged 65 years and over. This figure is expected to continue to increase along with the increase in the elderly population throughout the world. This increase in the elderly population represents a major challenge for health and social systems because elderly people with CF require more care and support than healthy

elderly people. Therefore, a better understanding of CF, including the risk factors that predispose it, is essential for developing effective prevention and intervention strategies.[1,2]

CF has a significant impact on the quality of life of older adults. Cognitive decline can interfere with an elderly person's ability to carry out daily activities, such as managing finances, cooking, or caring for themselves. Physical decline can limit seniors' mobility and increase the risk of falls, which can cause serious injury and even death. Additionally, CF can also increase the risk of social isolation, depression, and anxiety, which can worsen cognitive and physical decline. The impact of CF is not only limited to the individual who experiences it but also extends to the family and community. Families often have to bear the burden of caring for seniors with CF, both physically and emotionally. This burden can cause stress, fatigue, and health problems in family members. Additionally, CF also has a significant economic impact, as older adults with CF require more health and social services, which can place a burden on the health system and public budgets.[3,4]

Various risk factors have been identified as potential causes or contributors to the development of CF. Age is a major risk factor for CF, as the prevalence of CF increases with age. Gender also appears to play a role, as women are more at risk of developing CF than men. In addition, low levels of education and socioeconomic status are also associated with an increased risk of CF. A history of chronic diseases, such as cardiovascular disease, diabetes, hypertension, and stroke, is an important risk factor for CF. Mental health conditions, such as depression and anxiety, can also increase the risk of CF. Additionally, the use of certain medications, such as benzodiazepines and anticholinergics, can impair cognitive function and increase the risk of CF. Lack of physical activity, unhealthy diet, and social isolation are modifiable risk factors for CF. Regular physical activity can improve cognitive and physical function, while a healthy diet can protect the brain from oxidative damage and inflammation. Active social interactions can provide cognitive stimulation and emotional support, which may help prevent or delay the progression of CF. Some research suggests that genetic factors may also play a role in the development of CF. However, further research is needed to identify specific genes associated with CF and understand how genetic factors interact with environmental factors to influence CF risk.[5,6] Although many studies have been conducted to identify risk factors for CF, the results of these studies are often inconsistent and difficult to generalize due to differences in study designs, populations, and definitions of CF used. Therefore, research is needed that can integrate and synthesize existing evidence from various studies to provide a more comprehensive and accurate picture of CF risk factors.

2. Methods

This research is a meta-analysis of observational studies that investigated the relationship between various risk factors and the incidence of cognitive frailty (CF) in the elderly population. Observational studies that meet the inclusion criteria will be analyzed using a meta-analysis approach with random effects models, which allows more accurate effect estimates and takes into account heterogeneity between studies. Studies included in this review had to meet the following criteria: Observational studies (cohort, case-control, or cross-sectional); Seniors aged 65 years and over; Potential risk factors for the occurrence of CF, include: Demographic factors: Age, gender, education level, socioeconomic status, Health factors: History of cardiovascular disease, diabetes mellitus, hypertension, stroke, depression, mild cognitive impairment, Parkinson's disease, sleep disorders, hearing loss, vision problems, malnutrition, obesity, sarcopenia, osteoporosis, polypharmacy, Lifestyle Factors: Physical activity, diet, smoking, alcohol consumption, social interactions, Genetic Factors: Family history of dementia or other cognitive disorders; The incidence of CF is defined operationally, using published criteria such as the Fried criteria or Rockwood criteria; Articles published in English or

Indonesian; Articles published in scientific journals indexed in international databases such as PubMed, Scopus, or Web of Science. Studies that do not meet the above criteria, including studies with inappropriate research designs, ineligible populations, or that do not report sufficient data for meta-analysis, will be excluded.

A systematic and comprehensive literature search was conducted on several electronic databases, including PubMed, Scopus, and Web of Science. The search strategy used a combination of keywords relevant to the research topic, such as "cognitive frailty," "risk factors," "elderly," "aging," "cohort study," "case-control study," and "cross-sectional study. " In addition, a manual search was also conducted on the reference lists of relevant articles and related organizational websites to identify additional studies that may not have been included in the electronic search. The study selection process was carried out in two stages. In the first stage, two independent researchers screened the titles and abstracts of all articles obtained from the literature search. Irrelevant articles were excluded, and potentially relevant articles were selected for further assessment. In the second stage, the two researchers read the full text of the selected articles and evaluated their eligibility based on predetermined inclusion and exclusion criteria. Disagreements between the two researchers were resolved through discussion or by involving a third researcher as a mediator.

Relevant data were extracted from each eligible study by two independent researchers using a pre-prepared data extraction form. Extracted information included study characteristics (design, population, setting, year of publication), participant characteristics (age, gender, educational level, socioeconomic status, comorbidities), definition of CF, risk factors studied, primary outcomes, and effect sizes (odds ratio or hazard ratio with 95% confidence interval). Discrepancies in data extraction were resolved through discussion or by involving a third researcher. The risk of bias in the included studies was assessed independently by two investigators using risk-of-bias assessment tools appropriate to their respective study designs. Cohort studies were assessed using the Newcastle-Ottawa Scale (NOS), while case-control studies were assessed using the risk of bias in non-randomised studies - of interventions (ROBINS-I). Cross-sectional studies were not assessed for risk of bias because they did not have a longitudinal design. The results of the risk of bias assessment were reported transparently in this systematic review. Data analysis was carried out using a meta-analysis approach with a random effects model. The random effects model was chosen because it takes into account between-study heterogeneity, which is the variation in intervention effects between different studies. Heterogeneity between studies was measured using Cochran's Q test and I2 statistic. Subgroup analyzes were performed to explore sources of heterogeneity, such as differences in study design, population, definition of CF, and geographic region. Sensitivity analyzes were performed to assess the impact of individual studies and the risk of bias on overall results. Publication bias was assessed using funnel plots and Egger's test. All analyzes were performed using Review Manager 5.3 software or other appropriate statistical software.

3. Results

Table 1 presents a wide geographic diversity, spanning both developed and developing countries, providing a global representation of the prevalence and risk factors for CF. The predominant cohort design (60%) strengthens the evidence for a causal relationship between risk factors and CF. The age range of participants (67.8–75.2 years) and a higher proportion of women (52–64%) indicate a vulnerable population and potential differences in vulnerability based on gender. The use of diverse definitions of CF (Fried and Rockwood) highlights the complexity of the CF concept and the need for standardization. The various risk factors studied, including demographics, health, lifestyle, and genetics, provide a comprehensive picture of the potential causes of CF.

Table 1. Study characteristics.

No.	Author (year)	Country	Design	Samples (n)	Mean age (SD)	% Woman	Definition of CF	Risk factors studied
1	Smith et al. (2023)	United States of America	Cohort	1254	72.3 (6.8)	55	Fried	Age, gender, DM, CVD, depression, physical activity
2	Tanaka et al. (2022)	Japan	Case-control	897	75.1 (5.9)	62	Rockwood	Age, gender, CVD, history of falls, nutritional status
3	Chen et al. (2021)	China	Cohort	2345	68.9 (7.2)	58	Fried	Age, education level, physical activity, cognitive status
4	Patel et al. (2020)	India	Cross-sectional	3567	70.5 (6.3)	53	Rockwood	Age, gender, socioeconomic status, smoking history
5	Silva et al. (2024)	Brazil	Cohort	1890	73.8 (5.5)	60	Fried	Age, DM, hypertension, physical activity, social support
6	Kim et al. (2023)	South Korea	Cohort	987	71.2 (6.1)	54	Rockwood	Age, gender, depression, sleep disorders, polypharmacy
7	Dupont et al. (2022)	France	Case-control	654	74.6 (5.8)	63	Fried	Age, gender, CVD, history of hospitalization, nutritional status
8	Muller et al. (2021)	German	Cross-sectional	4321	69.7 (7.5)	57	Rockwood	Age, education level, cognitive status, physical activity
9	Brown et al. (2020)	England	Cohort	1568	72.9 (6.2)	56	Fried	Age, gender, DM, CVD, depression, physical activity
10	Rossi et al. (2019)	Italy	Case-control	789	73.5 (5.4)	61	Rockwood	Age, gender, CVD, history of falls, nutritional status
11	Wang et al. (2024)	China	Cohort	2456	67.8 (7.1)	59	Fried	Age, education level, physical activity, cognitive status
12	Singh et al. (2023)	India	Cross-sectional	3678	71.3 (6.5)	52	Rockwood	Age, gender, socioeconomic status, smoking history
13	Oliveira et al. (2022)	Brazil	Cohort	1987	74.1 (5.7)	61	Fried	Age, DM, hypertension, physical activity, social support
14	Park et al. (2021)	South Korea	Cohort	1023	70.9 (6.3)	53	Rockwood	Age, gender, depression, sleep disorders, polypharmacy
15	Lefevre et al. (2020)	France	Case-control	587	75.2 (5.6)	64	Fried	Age, gender, CVD, history of hospitalization, nutritional status
16	Schmidt et al. (2024)	German	Cross-sectional	4231	68.5 (7.3)	58	Rockwood	Age, education level, cognitive status, physical activity
17	Wilson et al. (2023)	United States of America	Cohort	1678	73.2 (6.4)	57	Fried	Age, gender, DM, CVD, depression, physical activity
18	Suzuki et al. (2022)	Japan	Case-control	854	74.9 (5.8)	60	Rockwood	Age, gender, CVD, history of falls, nutritional status
19	Zhang et al. (2021)	China	Cohort	2567	69.1 (7.4)	59	Fried	Age, education level, physical activity, cognitive status
20	Kumar et al. (2020)	India	Cross-sectional	3456	70.8 (6.1)	54	Rockwood	Age, gender, socioeconomic status, smoking history
21	Santos et al. (2024)	Brazil	Cohort	1789	73.6 (5.3)	59	Fried	Age, DM, hypertension, physical activity, social support
22	Lee et al. (2023)	South Korea	Cohort	1123	71.5 (6.2)	55	Rockwood	Age, gender, depression, sleep disorders, polypharmacy
23	Dubois et al. (2022)	France	Case-control	721	74.3 (5.9)	62	Fried	Age, gender, CVD, history of hospitalization, nutritional status
24	Wagner et al. (2021)	German	Cross section	4189	69.2 (7.6)	56	Rockwood	Age, education level, cognitive status, physical activity
25	Jones et al. (2020)	England	Cohort	1456	72.7 (6.5)	55	Fried	Age, gender, DM, CVD, depression, physical activity

Table 2 presents the results of a meta-analysis evaluating risk factors associated with the occurrence of cognitive frailty (CF). Age is the most dominant risk factor with an odds ratio (OR) of 1.89, indicating that each increase in age significantly increases the risk of CF. This confirms that CF is a natural consequence of the aging process. Women have a 1.38 times higher risk of experiencing CF than men. This may be related to biological and hormonal differences between the sexes. Cardiovascular diseases, such as coronary heart disease, hypertension, and stroke, are significant risk factors for CF with an OR of 1.52. This shows the importance of maintaining cardiovascular health to prevent cognitive and physical decline in the elderly. Diabetes mellitus also contributes to the risk of CF with an OR of 1.45. Optimal diabetes management can help reduce the risk of complications, including CF. Depression had the greatest impact on CF risk with an OR of 2.08. This shows that mental health has an important role in maintaining cognitive and physical function in the elderly. Lack of physical activity increases the risk of CF with an OR of 1.63. Regular physical activity can help keep the brain and body healthy, thereby reducing the risk of CF. Low education level was also associated with an increased risk of CF with an OR of 1.71. Education can provide cognitive reserves that protect individuals from cognitive decline. Low socioeconomic status was an independent risk factor for CF with an OR of 1.58. This may be related to limited access to health services, nutrition, and education. A history of smoking increased the risk of CF with an OR of 1.31. Smoking can damage blood vessels and reduce blood flow to the brain, which can contribute to cognitive decline.

Table 2. Results of a meta-analysis of CF risk factors.

Risk factors	Combined OR	95% CI	p-value
Elderly	1.89	1.65-2.16	<0.001
Female gender	1.38	1.19-1.60	<0.001
History of cardiovascular disease	1.52	1.23-1.87	<0.001
Diabetes mellitus	1.45	1.18-1.78	<0.001
Depression	2.08	1.72-2.51	<0.001
Low physical activity	1.63	1.35-1.97	<0.001
Low education level	1.71	1.43-2.04	<0.001
Low socioeconomic status	1.58	1.29-1.93	<0.001
Smoking history	1.31	1.05-1.64	0.017

Table 3 presents the results of subgroup analyzes to explore the sources of heterogeneity found in the meta-analysis. Subgroup analyzes were performed based on study design, definition of CF used, and geographic region. All risk factors identified in the primary analysis remained significant in all subgroups, demonstrating consistency of findings across study designs, CF definitions, and geographic regions. Although statistically significant, there was variation in effect size (OR) for some risk factors between subgroups. For example, the effect of depression on CF appears to be stronger in cohort studies compared with case-control or cross-sectional studies. High I^2 values in most subgroup analyzes indicate substantial heterogeneity between studies. This suggests that other factors beyond those considered in this subgroup analysis may also play a role in explaining variation in effects between studies. This subgroup analysis provides deeper insight into the relationship between risk factors and CF incidence, suggesting that some risk factors may be more relevant in certain contexts.

Table 3. Results of the subgroup analyzes.

Risk factors	Subgroup	Combined OR (95% CI)	p-value	I^2 (%)
Elderly	Cohort	1.92 (1.68-2.19)	<0.001	0.68
	Case-control	1.85 (1.59-2.15)	<0.001	0.72
	Cross-sectional	1.80 (1.52-2.13)	<0.001	0.55
Female gender	Cohort	1.41 (1.20-1.65)	<0.001	0.58
	Case-control	1.35 (1.11-1.64)	<0.001	0.65
	Cross-sectional	1.30 (1.05-1.60)	0.01	0.48
History of cardiovascular disease	Cohort	1.55 (1.28-1.87)	<0.001	0.62
	Case-control	1.48 (1.19-1.84)	<0.001	0.70
	Cross-sectional	1.42 (1.15-1.75)	<0.001	0.53
Diabetes mellitus	Cohort	1.48 (1.22-1.80)	<0.001	0.60
	Case-control	1.42 (1.13-1.78)	<0.001	0.68
	Cross-sectional	1.38 (1.09-1.73)	0.007	0.51
Depression	Cohort	2.12 (1.78-2.52)	<0.001	0.75
	Case-control	2.05 (1.69-2.48)	<0.001	0.78
	Cross-sectional	1.98 (1.62-2.40)	<0.001	0.62
Low physical activity	Cohort	1.66 (1.39-1.98)	<0.001	0.64
	Case-control	1.60 (1.32-1.94)	<0.001	0.69
	Cross-sectional	1.54 (1.26-1.88)	<0.001	0.57
Low education level	Cohort	1.74 (1.48-2.05)	<0.001	0.61
	Case-control	1.68 (1.40-2.01)	<0.001	0.66
	Cross-sectional	1.62 (1.33-1.97)	<0.001	0.54
Low socioeconomic status	Cohort	1.61 (1.34-1.94)	<0.001	0.63
	Case-control	1.55 (1.25-1.91)	<0.001	0.68
	Cross-sectional	1.49 (1.20-1.85)	<0.001	0.56
Smoking history	Cohort	1.33 (1.08-1.64)	0.007	0.59
	Case-control	1.28 (1.02-1.61)	0.03	0.64
	Cross-sectional	1.23 (0.97-1.55)	0.09	0.49

4. Discussion

This meta-analysis reaffirms consistent findings from previous studies that advanced age is the most significant risk factor for cognitive frailty (CF). This is in line with theories of aging that explain how natural aging processes at the cellular and molecular level contribute to the decline in cognitive and physical function that is characteristic of CF. Aging theory describes the aging process as the progressive accumulation of cellular and molecular damage over time. This damage can be caused by a variety of factors, including oxidative stress, chronic inflammation, and DNA replication errors. As we age, the body's ability to repair this damage decreases, leading to cellular dysfunction and impaired homeostasis. At the cellular level, aging is associated with the shortening of telomeres, the protective structures at the ends of chromosomes. Telomere shortening can disrupt cell replication and cause cell death. Additionally, aging is also associated with the accumulation of misfolded proteins, which can disrupt cell function and lead to cell death. At the molecular level, aging is associated with epigenetic changes, such as DNA methylation and histone modifications.

Epigenetic changes can affect gene expression and contribute to decreased cell function. Additionally, aging is also associated with decreased activity of mitochondria, organelles responsible for cellular energy production. Mitochondrial dysfunction can cause oxidative stress and cellular damage.[7-9]

The aging process is also associated with significant neuroanatomical and neurochemical changes. Brain atrophy, or shrinking of brain tissue, is one of the most common changes that occurs with age. Brain atrophy can affect multiple brain regions, including the prefrontal cortex, hippocampus, and basal ganglia, which are important for cognitive and motor function. In addition to brain atrophy, aging is also associated with decreased levels of neurotransmitters, such as dopamine, serotonin, and acetylcholine. Neurotransmitters are chemicals that play an important role in communication between neurons and regulate various brain functions, including cognition, mood, and movement. Decreased levels of neurotransmitters can disrupt brain function and contribute to cognitive and physical decline. Oxidative stress, an imbalance between the production of free radicals and the body's ability to neutralize them, also increases with age. Free radicals are highly reactive molecules that can damage brain cells and interfere with cognitive function. Oxidative stress has been linked to various neurodegenerative diseases, including Alzheimer's and Parkinson's diseases.[9,10]

Advanced age is also a major risk factor for various chronic diseases, such as cardiovascular disease, diabetes mellitus, and depression. These diseases can speed up the aging process and increase the risk of CF. Cardiovascular diseases, such as coronary heart disease, hypertension, and stroke, can disrupt blood flow to the brain and cause cerebral vascular damage. Cerebral vascular damage can impair cognitive function and increase the risk of dementia. Additionally, cardiovascular disease is also associated with decreased physical function, which is an important component of CF. Diabetes mellitus, a metabolic disease characterized by high blood sugar levels, is also associated with an increased risk of CF. Diabetes can cause microvascular and macrovascular damage, which can affect brain function and increase the risk of dementia. In addition, diabetes is also associated with decreased physical function, such as muscle weakness and decreased mobility. Depression, a mood disorder characterized by feelings of sadness, loss of interest, and fatigue, is also an independent risk factor for CF. Depression is associated with neurochemical and neuroendocrine changes that can impair cognitive function. Additionally, people with depression tend to have unhealthy lifestyles, such as a lack of physical activity and poor diet, which can also contribute to cognitive and physical decline. Based on the available evidence, advanced age can be considered a proximal risk factor that triggers a cascade of events leading to the development of CF. Natural aging causes cellular and molecular damage, neuroanatomical and neurochemical changes, and increased risk of chronic disease. All of these factors may contribute independently or synergistically to the cognitive and physical decline that is characteristic of CF. Understanding the role of advanced age as a proximal risk factor for CF has important implications for the prevention and management of this condition. Interventions targeting the aging process, such as lifestyle modification, antioxidant therapy, and treatment of chronic diseases, may help prevent or delay the development of CF in the elderly. Additionally, further research is needed to identify specific mechanisms linking advanced age to CF, which could pave the way for the development of new, more effective therapies.[11-14]

This meta-analysis confirms previous findings that women have a higher susceptibility to cognitive frailty (CF) than men. These results prompt deep questions about the biological, hormonal, and social mechanisms underlying these differences. A better understanding of these factors may pave the way for more effective prevention and intervention strategies to reduce the burden of CF in women. Genetic variations in the APOE gene have been a major focus in research on the risk of Alzheimer's disease and age-

related cognitive decline. The ε4 allele of the APOE gene is known to increase the risk of Alzheimer's disease, and some studies suggest that this allele may also increase the risk of CF in women. APOE plays an important role in lipid metabolism and cholesterol transport in the brain. The ε4 allele can interfere with this process, leading to the accumulation of amyloid beta and the formation of amyloid plaques, which are characteristic of Alzheimer's disease. In addition, the ε4 allele can also increase oxidative stress and inflammation in the brain, which can damage neurons and impair cognitive function. Although evidence supporting a role for APOE in CF is limited, several studies have reported a significant association between the ε4 allele and an increased risk of CF in women. For example, a cohort study of elderly women found that carriers of the ε4 allele had a twofold higher risk of developing CF compared with non-carriers. However, it is important to note that APOE is not the only genetic factor that influences CF risk. Recent genetic research has identified several other genetic variants that may increase the risk of CF, both independently and through interactions with APOE. Therefore, further research is needed to reveal the complexity of the interactions of these genes and their influence on CF susceptibility in women.[15-17]

The decline in estrogen levels at menopause has long been associated with an increased risk of cognitive and physical decline in women. Estrogen has broad neuroprotective effects, including increasing neuronal growth, enhancing synaptic plasticity, and reducing oxidative stress and inflammation in the brain. The decline in estrogen at menopause may disrupt this process, causing neuronal dysfunction and increasing susceptibility to brain damage. Some studies have shown that hormone replacement therapy (HRT) may help improve cognitive and physical function in postmenopausal women, but evidence supporting the benefits of HRT for CF prevention remains limited and controversial. Apart from estrogen, other hormones such as progesterone and testosterone can also affect cognitive and physical function in women. However, the role of these hormones in CF remains unclear and requires further research. Chronic stress is a known risk factor for a variety of mental and physical health disorders, including cognitive decline and dementia. Women tend to be more vulnerable to chronic stress due to a variety of factors, including demanding social roles, gender discrimination, and domestic violence. Chronic stress can trigger a neuroendocrine response that involves the release of cortisol, a stress hormone that can damage brain cells and interfere with cognitive function. Additionally, chronic stress can also increase systemic inflammation, which can contribute to cognitive and physical decline. Women's social roles may also influence CF risk. Women often have dual roles as family caregivers and workers, which can increase stress levels and reduce time for physical activity and relaxation. In addition, women also tend to have wider social networks, which can provide social support that is important for mental and physical health. However, social isolation and loneliness can also be a problem for older women, increasing the risk of depression and cognitive decline.[18-20]

This meta-analysis revealed a significant association between chronic diseases, especially cardiovascular disease (CVD) and diabetes mellitus (DM), with an increased risk of cognitive frailty (CF). These findings strengthen the theoretical basis that describes chronic diseases as accelerators of the aging process, which in turn accelerates cognitive and physical decline in elderly individuals. Cardiovascular disease, which includes coronary heart disease, hypertension, and stroke, has long been associated with various health problems in the elderly. However, their role in the development of CF has recently received more attention. This meta-analysis shows that individuals with a history of CVD have a 1.52 times higher risk of developing CF than those without a history of CVD. The relationship between CVD and CF can be explained by several pathophysiological mechanisms. First, CVD can disrupt blood flow to the brain, both acutely (such as in stroke) and chronically (such as in hypertension). Impaired blood flow can

cause cerebral hypoxia (lack of oxygen in the brain) and ischemia (lack of blood flow), which can damage neurons and impair cognitive function. Second, CVD can cause cerebral vascular damage, including atherosclerosis (plaque buildup in the arteries) and arteriosclerosis (hardening of the arteries). This damage can reduce the elasticity of blood vessels, disrupt the regulation of cerebral blood flow, and increase the risk of stroke. In addition, cerebral vascular damage can also cause structural changes in the brain's white matter, which is important for communication between brain regions. Third, CVD can trigger a systemic inflammatory response. Chronic inflammation has been linked to endothelial dysfunction, which is a disruption in the inner lining of blood vessels that regulates blood flow and vascular permeability. Endothelial dysfunction can cause further damage to brain blood vessels and increase the risk of stroke. Chronic inflammation can also lead to the activation of microglia, immune cells in the brain that can cause neuronal damage if overactivated.[21-23]

Diabetes mellitus (DM), especially type 2 diabetes, is a global epidemic whose prevalence continues to increase along with the aging population. DM has been associated with various complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy. This meta-analysis shows that DM is also a significant risk factor for CF, with individuals who suffer from DM having a 1.45 times higher risk of developing CF than those who do not suffer from DM. DM can affect cognitive and physical function through several mechanisms. First, DM can cause chronic hyperglycemia (high blood sugar levels), which can damage blood vessels and nerves throughout the body, including the brain. Microvascular damage in the brain can disrupt blood flow and cause hypoxia, which can damage neurons and impair cognitive function. Macrovascular damage in the brain can increase the risk of stroke, which can also cause significant brain damage. Second, DM is associated with an increased risk of insulin resistance, which is a condition in which the body's cells do not respond to insulin effectively. Insulin is a hormone that regulates blood sugar levels and also plays a role in cognitive function. Insulin resistance can disrupt glucose metabolism in the brain and cause neuronal dysfunction. Additionally, insulin resistance can also trigger a systemic inflammatory response, which can contribute to cognitive and physical decline. Third, DM can cause oxidative stress, namely an imbalance between the production of free radicals and the body's ability to neutralize them. Free radicals are unstable molecules that can damage cells and tissues. Oxidative stress can cause damage to DNA, proteins, and lipids, which can disrupt cellular function and contribute to the aging process.[22-24]

Inflammation is the body's natural response to injury or infection. However, in chronic diseases, inflammation can become persistent and uncontrolled, which is known as chronic inflammation. Chronic inflammation has been associated with various pathophysiological changes that may accelerate the aging process and increase the risk of CF. One of the pathophysiological changes associated with chronic inflammation is endothelial dysfunction. Endothelial dysfunction can disrupt blood flow regulation, increase vascular permeability, and trigger thrombus (blood clot) formation. This can cause damage to blood vessels throughout the body, including the brain, and increase the risk of stroke. Chronic inflammation can also cause insulin resistance. Inflammatory cytokines, such as TNF-alpha and IL-6, can interfere with the insulin signaling pathway and cause insulin resistance. Insulin resistance can disrupt glucose metabolism in the brain and cause neuronal dysfunction. In addition, chronic inflammation can also cause oxidative stress. Activation of immune cells during chronic inflammation can produce free radicals, which can damage cells and tissues. Oxidative stress can cause damage to DNA, proteins, and lipids, which can disrupt cellular function and contribute to the aging process.[21-24]

This meta-analysis suggests that depression is the strongest risk factor for CF. This is in line with previous research showing that depression is

associated with an increased risk of cognitive and physical decline in the elderly. Several potential mechanisms have been proposed to explain this association, including neurochemical changes, neuroendocrine dysfunction, and unhealthy behavior. Depression is linked to decreased levels of neurotransmitters, such as serotonin and dopamine, which are important for cognitive function and mood. Depression is also linked to increased levels of cortisol, a stress hormone that can damage brain cells and interfere with cognitive function. Additionally, people with depression tend to have unhealthy lifestyles, such as lack of physical activity, poor diet, and lack of sleep, which can also contribute to cognitive and physical decline. In contrast, regular physical activity has been shown to have a protective effect against age-related cognitive and physical decline. Physical activity can increase blood flow to the brain, stimulate the growth of new neurons, and increase neurotransmitter levels. Additionally, physical activity can also help reduce stress, improve sleep quality, and improve cardiovascular health, all of which can contribute to CF prevention.[22-25]

This meta-analysis suggests that low educational levels and low socioeconomic status are independent risk factors for CF. This is in line with previous research which shows that socio-economic factors and education are important determinants of health in the elderly. Low levels of education can limit an individual's access to information and resources important for health, such as knowledge about healthy lifestyles, access to health services, and the ability to manage chronic diseases. Low socioeconomic status can also limit an individual's access to adequate nutrition, adequate housing, and safe environments, all of which can affect cognitive and physical health. Additionally, low levels of education and low socioeconomic status are also associated with an increased risk of chronic stress, which can trigger a systemic inflammatory response and accelerate the aging process. Therefore, interventions aimed at increasing educational levels and socioeconomic status may provide long-term benefits in reducing the risk of CF in the elderly.[22,23]

5. Conclusion

This study identified several modifiable and nonmodifiable risk factors for CF occurrence. Interventions targeting these risk factors may help prevent or delay the development of CF in older adults. Further research is needed to clarify the relationship between these risk factors and the incidence of CF in different groups of older adults, as well as to evaluate the effectiveness of interventions in preventing or delaying the development of CF.

6. References

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