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Heart disease Risk Factors and the Chance of Getting Alzheimer's in the Future

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Abstract

Alzheimer's disease (AD), currently lacking a recognized cure, is a neurological condition that disproportionately affects the elderly population. Although cerebrovascular pathology is also common, Alzheimer's disease is primarily characterized by the presence of senile plaques and neurofibrillary tangles. In this review, we present literature that examines the relationship between risk factors and cardiovascular disease (CVD) in the progression of Alzheimer's disease (AD). Initially, we will examine the correlation between Alzheimer's disease and clinical cardiovascular illnesses, including heart disease and stroke. Subsequently, we will provide a concise summary of the correlation between Alzheimer's disease and imaging indicators of pre-clinical vascular disease. Ultimately, we will examine the correlation between Alzheimer's disease and the risk factors associated with cardiovascular disease. We examine both the established risk factors for cardiovascular disease, as well as the recently

identified potential risk variables that have a partial impact on cardiovascular disease.

Keywords: Cardiovascular disease, Imaging markers, Risk factors, Dementia, Alzheimer's disease

Introduction

Alzheimer's disease (AD), which currently lacks a recognized cure, is a neurological illness that primarily affects the older population. While cerebrovascular pathology may also occur, Alzheimer's disease is primarily distinguished by the presence of senile plaques and neurofibrillary tangles. This review focuses on the existing literature that investigates the correlation between risk factors and cardiovascular disease (CVD) in the advancement of Alzheimer's disease (AD). Firstly, we will investigate the association between Alzheimer's disease and clinical cardiovascular conditions, such as heart disease and stroke. Next, we will present a brief overview of the relationship between Alzheimer's disease and imaging markers of pre-clinical vascular disease. In the end, we will investigate the connection between Alzheimer's disease and the risk factors linked to cardiovascular disease. We analyze both the well-established risk factors for cardiovascular disease, as well as the newly discovered potential risk variables that have a partial influence on cardiovascular disease.

Review

Cardiovascular disease

Cardiovascular disorders (CVDs) such as heart failure, coronary heart disease (CHD), atrial fibrillation, stroke, and others are prevalent in older adults and have often been associated with Alzheimer's disease (AD). Cardiovascular disease is recognized for its ability to promote reduced blood flow and the formation of small blood clots, both of which have been linked to the onset of Alzheimer's disease [10,11]. Hence, apart from the potential existence of shared risk factors between cardiovascular diseases and Alzheimer's disease, there might also be a

direct causal link between the two. In the subsequent sections, we will examine the latest research that establishes a connection between prevalent cardiovascular disorders and the susceptibility to Alzheimer's disease.

Stroke

Although this form of dementia is usually known as "post-stroke dementia" or "vascular dementia" according to its description [12], there is a strong correlation between experiencing dementia after a clinical stroke. The use of complex language hinders a thorough examination of the role that clinical stroke plays in Alzheimer's disease. Hence, investigating asymptomatic or "silent" stroke, typically lacunae, yields crucial information regarding the correlation between stroke and the onset of Alzheimer's disease. Multiple studies [13–15] have found that lacunae significantly contribute to the prevalence of dementia, particularly Alzheimer's disease. In addition, white matter lesions, which are a form of ischemic brain injury, have been linked to both Alzheimer's disease and cognitive function impairment [16, 17]. These data suggest that stroke is a contributing factor to the chance of getting dementia. To elucidate this association, the following mechanisms are implicated. Firstly, the detrimental effects of neuronal tissue degeneration induced by tau and amyloid disease can be worsened by the loss of neuronal tissue resulting from a stroke [15]. There is a suggestion that cerebrovascular disease has a direct impact on amyloid pathology by either increasing the production of amyloid β or impeding its removal [3,18–21]. This is in spite of the fact that research on both pathways is very undeveloped.

Atrial fibrillation

Several studies have demonstrated a correlation between atrial fibrillation (AF) and an increased susceptibility to Alzheimer's disease (AD), as well as a higher likelihood of developing the condition [22–24]. The association between atrial fibrillation and Alzheimer's disease may be elucidated by the occurrence of clinical or silent stroke, as atrial fibrillation can lead to embolisms that can result

in strokes [10,25–27]. According to a meta-analysis, only individuals who had already experienced a stroke showed a consistent association between atrial fibrillation and an increased risk of dementia [23]. In contrast, a separate study discovered that people diagnosed with atrial fibrillation, but who had not suffered a stroke, exhibited reduced hippocampal sizes and fared inadequately on memory and learning assessments [28]. The link between Alzheimer's disease and atrial fibrillation is probably mediated by distinct mechanisms [29]. The reason for this is the strong link between the size of the hippocampus and both memory function and the occurrence of Alzheimer's disease. There is a concept that proposes that reduced blood flow to the brain in individuals with atrial fibrillation leads to harm to nerve cells, which subsequently contributes to the progression of Alzheimer's disease [23–27]. Nevertheless, there is yet little evidence to substantiate this concept [30]. Another hypothesis posits that atrial fibrillation (AF) exerts a direct impact on the neuropathology of Alzheimer's disease (AD), characterized by the presence of neurofibrillary tangles and senile plaques.

Coronary heart disease

Congestive heart failure is a leading cause of death globally and is the most prevalent form of cardiac illness [31]. Treatments for coronary revascularization, myocardial infarction (MI), and angina pectoris are encompassed within the broader category of treatments for coronary heart disease (CHD). The presence of significant conflicting risks of mortality poses a challenge in distinguishing between coronary heart disease and Alzheimer's disease. Several research have demonstrated a link between coronary heart disease and cognitive impairment or Alzheimer's disease [32, 33], while other investigations have shown no correlation [34, 35]. According to the Rotterdam Study, whereas acknowledged myocardial infarction (MI) was not shown to be associated with the risk of Alzheimer's disease, unreported MI was found to have a connection [36]. One

rationale is that Alzheimer's disease and coronary heart disease have a common genesis, as atherosclerosis significantly contributes to the development of both conditions [26, 27]. The findings of the Cardiovascular Health Study [32] provide support for the idea that peripheral artery disease, a marker of atherosclerosis, is strongly associated with a higher chance of developing Alzheimer's disease. Alzheimer's disease in coronary heart disease is also linked to a decrease in cardiac function, reduced blood flow, and the presence of emboli [10–27].

Heart failure

Heart failure is a medical disorder where the heart's ability to pump blood is reduced, resulting in insufficient blood flow throughout the body. There is a proven association between Alzheimer's disease and heart failure [37–39]. A Swedish study [37] has found a correlation between heart failure and a higher likelihood of developing dementia, including Alzheimer's disease. Furthermore, the aforementioned study revealed that the implementation of anti-hypertensive pharmaceutical therapy led to a little decrease in the likelihood of developing this illness. The Framingham Offspring Study [40] revealed a correlation between reduced brain volume, a significant marker for dementia, and impaired cardiac function, even in persons without clinical heart failure. The mechanisms behind the relationship between heart failure and the development of Alzheimer's disease are similar to those that explain the origin of atrial fibrillation (AF). Heart failure causes reduced blood flow to the brain, resulting in a decrease in oxygen supply and the death of nerve cells [3,4,25–27]. Furthermore, it is worth noting that heart failure is linked to a higher likelihood of developing microvascular disease. This includes conditions such as white matter lesions, lacunae, and emboli, all of which are related with an elevated risk of dementia [10,25–27].

Pre-clinical markers of cardiovascular disease

Significant durations elapse before the identification of cardiovascular pathology occurs during a clinical episode. Similarly, the biology of Alzheimer's disease

progresses over several decades before the clinical symptoms become apparent. Several research have been undertaken to examine the correlation between Alzheimer's disease and pre-clinical pathology, as well as cognitive impairment.

Pre-clinical markers of large vessel disease

Various imaging modalities can be used to evaluate potential pre-clinical indicators of major vascular disease. Table 1 contains the measures of intima medium thickness (IMT) and carotid plaque. Alzheimer's disease is linked to a variety of probable vascular variables. Cardiac issues Preceding the beginning of heart disease, there are symptoms that serve as established risk factors for cardiovascular disease in the general population. Novel risk factors are arising that can contribute to the occurrence of a stroke. The proximity of the media's thickness A link exists among hypertension, blood pressure, and arterial stiffness. Provocative reply Arrhythmia in the carotid atrial arteries Diabetes mellitus and chronic kidney disease are metabolic diseases related to glucose. Cardiovascular conditions that impact the heart in the coronary arteries The presence of calcium cholesterol deposits in the arteries, caused by elevated thyroid activity, might lead to a heart attack. The existence of gaps and abnormalities in the white matter Cerebral hemorrhages resulting from tobacco usage Experiencing obesity Cerebral microinfarctions.

The lack of compliance with the Mediterranean diet and inadequate levels of physical activity Modifications to the blood vessels in the retina Homocysteine Ultrasonography is a method that can be used to determine the small-scale structure and connections of atherosclerosis in the carotid artery. Individuals afflicted with dementia and Alzheimer's disease exhibit a higher prevalence of both intramural tangles and carotid plaque [41], when compared to individuals with normal cognitive function. Moreover, there exists a correlation between these characteristics and an elevated susceptibility to cognitive impairment in individuals diagnosed with Alzheimer's disease [42]. Moreover, some studies

conducted on a community level have demonstrated that persons with the highest measurements of intima-media thickness (IMT) are more likely to develop incident dementia, including Alzheimer's disease [32, 43, 44]. One study [44] found that scores on the carotid plaque were linked to a higher risk of Alzheimer's disease. However, this association did not reach a statistically significant level. Computed tomography (CT) can be used to measure the volume of calcification in the atherosclerotic plaque, which is an indicator of pre-clinical big vessel disease.

Although calcification is a minor component of plaque, it consistently provides a reliable measure of the total plaque burden [45]. One drawback of computed tomography (CT) is its radiation exposure to patients. However, unlike ultrasonography, CT assessments of atherosclerotic calcification are less reliant on the observer. Several investigations have discovered an inverse relationship between decreased cognitive performance and increased levels of calcification in the coronary, aortic, and carotid arteries [46, 47]. However, it should be noted that there has been a scarcity of study undertaken on the correlation between dementia and atherosclerotic calcification as observed by CT scans. Moreover, a relationship was observed between higher volumes of calcification and smaller volumes of brain tissue, together with a deterioration in the structural integrity of white matter [46]. There is a positive association between these two factors and a higher likelihood of acquiring Alzheimer's disease. Several pathways connect carotid artery disease to Alzheimer's disease [3,4,6]. Several mechanisms that will be further explained include hypoperfusion, common etiology, and sub-clinical cerebral small vessel disease.

Pre-clinical markers of cerebral small vessel disease

Multiple studies have shown ample evidence connecting Alzheimer's disease (AD) or cognitive impairment to structural imaging markers of cerebral small artery disease, including lacunae and white matter lesions [15–17, 48–50]. Moreover,

studies have demonstrated that cardiovascular disease has a partial impact on brain atrophy, which is a recognized indicator of dementia and Alzheimer's disease [48, 51, 52]. Cerebral microbleeds (CMBs), commonly referred to as brain microbleeds, are a newly identified vascular indicator that has significant promise for Alzheimer's disease research. Given the association between vascular pathology and amyloid β in the development of cerebral microbleeds (CMBs), it is highly likely that there is a correlation between CMBs and the onset of Alzheimer's disease [53–55]. In order to confirm the presence of this connection, a longitudinal investigation is still required. Recent advancements in high-field magnetic resonance imaging (MRI) scanners, such as the 7 T scanner, have made it possible to detect cerebral microinfarcts. Although the exact significance of microinfarcts in Alzheimer's disease is not yet fully comprehended, it is anticipated that future research would prioritize the investigation of these microinfarcts [56,57]. Despite the ability to identify indicators of cerebral small artery disease, directly visualizing the small cerebral arterioles in living organisms remains challenging. Retinal imaging allows for convenient observation of retinal vessels, which originate from the same tissues as brain vessels throughout embryonic development. Retinal imaging enables in-vivo studies on the brain's small blood veins. The diameter of the retinal artery has been linked to several disorders, such as white matter lesions, infarcts, brain atrophy, and an elevated risk of vascular dementia [58–60]. Although a recent case-control study discovered an association between Alzheimer's disease and changes in the microvascular structure of the retina [61], there is now no evidence establishing a long-term connection between retinal vasculature and an elevated risk of Alzheimer's disease.

Measures of brain connectivity

Due to advancements in imaging techniques, it is now feasible to quantify more nuanced brain abnormalities, such as alterations in brain connectivity. DTI

assesses the microstructural coherence of the white matter. Research has demonstrated that DTI markers can indicate the initial phase of vascular brain illness. Several investigations have demonstrated a loss of microstructural integrity in early Alzheimer's disease (AD) or moderate cognitive impairment (MCI) [62–64]. However, there is a limited amount of longitudinal research that establishes a connection between DTI indicators and the presence of Alzheimer's disease. A novel form of MRI scan examines the functional connectivity of the brain during periods of rest in order to determine the level of brain activity. Several research [65–69] have discovered altered functional connectivity in individuals with Alzheimer's disease (AD) and mild cognitive impairment (MCI). However, there is currently a paucity of comprehensive longitudinal data on this topic. Furthermore, the connection between cardiovascular risk factors and functional MRI remains unclear.

Cardiovascular risk factors

In addition to clinical cardiovascular diseases (CVDs), AD has also been associated with risk factors for CVDs (as mentioned above). There is compelling evidence that establishes a direct connection between cardiovascular risk factors and AD. However, it is also possible that the causative pathway of these risk factors is associated with the development of clinical disease.

Blood pressure, hypertension, and arterial stiffness

Several investigations have demonstrated a correlation between hypertension and white matter abnormalities, neurofibrillary tangles, and brain atrophy [70 72]. Consequently, there is a potential correlation between Alzheimer's disease and hypertension. The nature of this relationship, however, is intricate and varies with age [73]. Although several research [74–77] have found a link between hypertension in older age and dementia, other studies have not found any connection between hypertension in midlife and an increased risk of Alzheimer's disease. Indeed, there is compelling evidence suggesting a potential association

between Alzheimer's disease and low blood pressure [73]. The onset of dementia is expected to be preceded by a decline in blood pressure, which can be attributed to a decrease in body weight and a lack of physical activity in the years leading up to the clinical manifestation of the disease. Nevertheless, the causes for these discrepancies have not been determined as of yet. Further study is required to validate this notion [27]. Arterial stiffness and hypertension have a robust association with blood pressure. Arterial stiffness refers to the measurement. There are two methods to measure it: either by an augmented pulse pressure or by an elevated pulse wave velocity. Arterial stiffness is a challenge to research due to its dual role in causing and resulting in hypertension [78,79].

Elevated pulsatile pressure, resulting from arterial stiffness, leads to harm in the microvascular system of the brain, consequently contributing to cognitive deterioration [80]. Several studies have found a correlation between a higher pulse pressure or a higher pulse wave velocity and an increased occurrence and risk of Alzheimer's disease (AD) or cognitive decline [81–83]. Nevertheless, further inquiries [84, 85] failed to show a correlation between these two variables.

Glucose metabolism and diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a complex disorder characterized by insulin resistance, elevated blood glucose levels, and subsequent damage to multiple organs due to impaired microvascular function. Type 2 diabetes has been linked to atherosclerosis and infarcts in the brain [86,87]. Several studies have demonstrated a positive correlation between type 2 diabetes and the likelihood of acquiring dementia and Alzheimer's disease [88]. Pre-diabetes, commonly referred to as borderline type 2 diabetes, is linked to a heightened susceptibility to Alzheimer's disease [89]. Aside from the harm caused to the microvascular system, another suggested connection between type 2 diabetes and Alzheimer's disease is the direct toxicity to the brain, resulting from high levels of insulin and glucose.

Elevated levels of glucose in the bloodstream have a negative impact on brain cells due to the generation of oxidative stress and protein glycation [88]. Given that insulin is vital for removing amyloid β from the brain, it is plausible that elevated insulin levels could interfere with this metabolic process, hence intensifying the accumulation of amyloid β [88].

Hypercholesterolemia

Given that cholesterol is involved in the removal of amyloid β, it has been proposed that having high levels of cholesterol is linked to a higher risk of developing Alzheimer's disease. An imaging study conducted recently [90] has provided the essential evidence to substantiate this hypothesis by demonstrating a link between increased levels of cholesterol and elevated levels of amyloid β. Furthermore, there is a strong correlation between elevated cholesterol levels and the existence of apolipoprotein E ε4-carrier status, which is well recognized as one of the most substantial genetic predispositions for Alzheimer's disease [91]. However, epidemiological research have yielded conflicting findings about the relationship between Alzheimer's disease and hypercholesterolemia. Several studies have found that hypercholesterolemia does not seem to be linked to a higher chance of developing Alzheimer's disease later in life. However, there is a connection between the two conditions throughout middle age [92]. One plausible hypothesis is that while reduced cholesterol levels in later stages of life may serve as an indicator of pre-clinical disease, elevated cholesterol levels in midlife pose a risk factor for the development of Alzheimer's disease. This is because individuals with sub-clinical dementia modify their dietary and lifestyle choices during the course of their lives.

Smoking

Several extensive studies [93] have established a clear link between smoking and the occurrence of Alzheimer's disease and dementia. Both the Rotterdam Study and the Honolulu-Asia Aging Study found that smokers had a higher probability

of getting dementia in comparison to non-smokers [94,95]. Furthermore, the Honolulu-Asia Aging Study discovered a direct correlation between the quantity of packyears and the accumulation of amyloid in the brain [95]. Smoking increases the likelihood of developing atherosclerosis, a condition that is also linked to the development of cerebral small artery disease [49,96]. Tobacco contains a substantial quantity of neurotoxins, which can directly harm neurons [97]. However, further investigation is necessary to determine the precise mechanisms that explain the link between alcohol intake and dementia.

Obesity

The correlation between hypertension and elevated cholesterol levels, as well as the correlation between obesity and dementia and the risk of Alzheimer's disease, is subject to age-related variations [98100]. Evidence suggests that individuals with a higher body weight experience a safeguarding effect as they grow older, but obesity at middle age is linked to a higher likelihood of developing dementia and Alzheimer's disease [100,101]. Due to changes in diet and lifestyle, individuals with sub-clinical dementia tend to gradually lose weight. Therefore, a low body weight can also serve as an early sign of dementia [98-100]. Conversely, being obese during middle age is linked to a higher likelihood of developing other chronic conditions, such as vascular diseases. Additionally, there may be a connection between obesity and an elevated risk of developing dementia and Alzheimer's disease through comparable biological mechanisms [101].

Mediterranean diet and physical activity

The defining features of the Mediterranean diet include a substantial intake of fruits, vegetables, grains, and unsaturated fats, a moderate intake of fish, poultry, eggs, red wine, and dairy products, and a limited intake of red meats, processed meats, and saturated fats [102]. Research has shown that following a Mediterranean diet can decrease oxidative stress and inflammation, as well as offer defense against cardiovascular disease and its risk factors [103]. Two recent

meta-analyses [104, 105] indicate that following a Mediterranean diet may lower the likelihood of getting Alzheimer's disease. However, there is a lack of studies with long-term follow-up periods. Therefore, further study is needed to confirm the potential preventative effects of the Mediterranean diet on Alzheimer's disease. Modifying physical exercise can be an additional measure to decrease the risk of Alzheimer's disease [9,106].

Dietary choices are also pertinent in this context. Engaging in regular exercise can potentially lower the likelihood of acquiring Alzheimer's disease [107,108], as there exists an inverse correlation between diabetes and physical activity. Conversely, engaging in physical activity has been proven to directly decrease the likelihood of getting dementia [109,110]. This is because it promotes the growth of new nerve cells and enhances blood flow in the brain. Several epidemiological studies have discovered an association between increased levels of physical activity and a reduced risk of dementia or cognitive decline [111–115]. Conversely, most of these investigations had relatively brief periods of follow-up, while studies with longer follow-up periods yielded inconclusive findings [115,116]. Regarding the levels of physical activity,

Homocysteine

Plasma homocysteine levels serve as a reliable indicator of the levels of vitamin B12 and folate in the body, and they are also associated with renal function. Research has confirmed that increased levels of homocysteine are linked to cardiovascular issues and can potentially impact the phosphorylation of tau and amyloid β. Therefore, elevated levels of homocysteine in the bloodstream have been linked to a higher likelihood of acquiring Alzheimer's disease [118]. Imaging and autopsy studies [119, 120] have identified a connection between increased levels of homocysteine and the formation of neurofibrillary tangles, as well as the shrinking of the brain. Nevertheless, not all of the published research corroborates these conclusions. A recent study discovered no correlation between

plasma homocysteine levels and Alzheimer's disease [121]. This finding was obtained after accounting for variables such as renal impairment, vitamin B12 or folate deficiencies, and other relevant parameters. In order to fully comprehend this correlation, further investigation is necessary.

Emerging risk factors

In addition to the classic vascular risk factors, there are other emerging risk factors that have been implicated in AD, partly by vascular mechanisms.

Inflammation

Research has confirmed that several indicators of inflammation are linked to a higher occurrence of dementia, including Alzheimer's disease [122–124]. Astrocytes and microglia activate the brain's immune system in response to the presence of pathogens, such as infections and cardiovascular disorders [125,126]. Several studies [127] have reported an increased presence of activated microglia surrounding senile plaques in the brains of both Alzheimer's disease (AD) transgenic animal models and patients. Moreover, it is important to mention that amyloid β has the capacity to activate the immune system of neurons, potentially resulting in a prolonged inflammatory reaction that is harmful to nerve cells [126]. Moreover, based on the latest discoveries in genetic research [128], some genes linked to inflammation and the immune system have been found to be connected to Alzheimer's disease. However, there is a lack of large-scale research that have examined the relationship between inflammation and Alzheimer's disease (AD) in the general population. Additionally, clinical trials exploring the impact of immunotherapy on Alzheimer's disease have not yielded promising outcomes thus far [126]. Therefore, further investigation is required to comprehend the exact role of inflammation in Alzheimer's disease.

Chronic kidney disease

In recent years, numerous research have been undertaken to examine the correlation between Alzheimer's disease (AD) or cognitive decline and chronic

kidney disease (CKD). While some of these studies [134] could not establish a link between reduced kidney function and a higher likelihood of dementia, Alzheimer's disease, or cognitive decline, the majority of the investigations [129–133] did confirm this association. Given the significant diversity in the kidney function metrics used in all research populations [132], it is plausible that these variations stem from changes in experimental methods. Dementia and chronic kidney disease (CKD) are connected through several mechanisms, including shared risk factors (such as obesity, smoking, arterial stiffness, and hypertension) and direct impacts of the disease (such as anemia, uremic toxins, hemodynamic abnormalities, and chronic inflammation) [129]. These processes are accountable for the association between dementia and CKD. Further investigation is necessary as these pathways remain incompletely comprehended.

Thyroid function

There is a potential for cognitive impairment to be reversed in situations of thyroid malfunction, due to the importance of thyroid hormone for maintaining healthy brain function [135]. Research has demonstrated that thyroid hormone can influence the regulation of amyloid precursor protein (APP). Animal study has demonstrated that hyperthyroidism causes an increase in the production of amyloid β, resulting in higher levels of amyloid β [135]. Moreover, due to the correlation between thyroid dysfunction and cardiovascular disease, it can potentially indirectly influence the causation of Alzheimer's disease [135]. Ultimately, the pathology of Alzheimer's disease leads to a decrease in the release of thyrotropin-releasing hormone, resulting in an alteration of thyroid hormone levels [136]. Observational studies have established a correlation between both hyperthyroidism and hypothyroidism and the occurrence of Alzheimer's disease (AD). Nevertheless, some of these experiments failed to establish a correlation between the two situations [136–140].

Conclusion

In summary, a growing collection of evidence indicates that cardiovascular diseases (CVDs) and the associated risk factors significantly contribute to the progression of Alzheimer's disease. Although the mechanisms connecting certain attributes to Alzheimer's disease are readily apparent, the correlation between others of these characteristics and the disease is more intricate and necessitates additional investigation to achieve a complete understanding. Conversely, at present, only the vascular variables are recognized as modifiable risk factors associated with Alzheimer's disease. Hence, further investigation is warranted to ascertain the feasibility of manipulating these variables with the intention of averting or postponing the progression of Alzheimer's disease.

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