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# The Triad of Atrial Fibrillation, Dementia, and Type 2 Diabetes: A Narrative Review of a Complex Interplay

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## Abstract

Dementia is on the rise as a public health burden and age-related atrial fibrillation (AF) and type 2 diabetes mellitus (T2DM) constitute two known substantial risk factors for dementia. In this review, we discuss the complex relationship between these three states and propose potential mechanisms for their association based on interactions among them; in addition, possible clinical implications are addressed. AF is a frequent heart rhythm disorder that has been repeatedly associated with an increased risk of dementia. The association is probably mediated via numerous mechanisms, including a common pathway such as stroke or shared risk factors (inflammation and vascular dysfunction) in addition to the direct effects of atrial fibrillation on cerebral blood flow and oxygenation. Type 2 diabetes (T2D), a metabolic disorder related to insulin resistance, is another risk factor of dementia that has been demonstrated independently. Type 3 diabetes" is a now commonly used term and indicates the possibility of Alzheimer's disease being associated with brain insulin resistance. Several candidate mechanisms have been proposed to account for the relationship between T2D and dementia, including a direct impact of insulin resistance on brain function impaired by hyperglycemia-induced oxidative stress/ inflammation or microvascular complications in cerebral blood vessels.

**Conclusions:** The combination of AF and T2D seems to be a risk factor potentiation for dementia, likely related to common cardiovascular risk factors, similar pathophysiological mechanisms as well as increased vulnerability toward the consequences of AF in diabetic patients. And this speaks to the importance of having an entire patient care package.

The second step is to make sure that AF among patients with T2D would not go undetected and untreated, as efficient control of modifiable risk factors including blood pressure, glycemia or lipid profile involves central measures in targeted glucose-lowering therapy; early detection and management matter. Even more importantly, this high-risk population needs personalized strategies for stroke prevention. Additional studies are necessary to understand better the intricate relationship among AF, T2D, and dementia. Furthermore, large-scale prospective studies are particularly necessary to determine the temporal relationships and causal pathways. In the long term, by better understanding how this interaction occurs, we may develop new therapies that target common pathways and ultimately reduce the rapidly expanding burden of dementia in these patients.

**Keywords:** Atrial fibrillation, Dementia, Type 2 diabetes mellitus, Cardiovascular disease, Cerebrovascular disease, Cognitive impairment, Inflammation, Oxidative stress, Comorbidities

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## Dementia and its Epidemiology

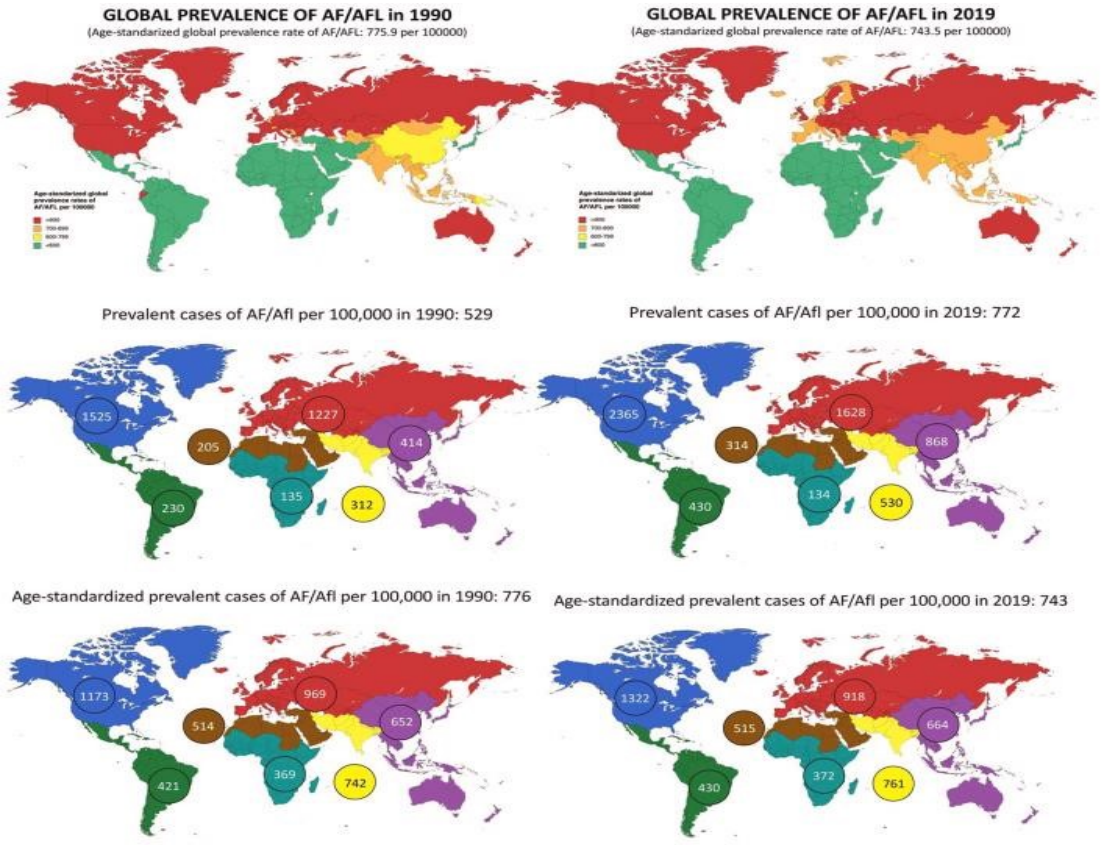
Dementia refers to a group of conditions characterized by a decline in cognitive function, including memory loss, impaired thinking, and difficulties with everyday tasks, ultimately affecting an individual's ability to live independently [1]. Dementia is currently the seventh most leading cause of death. Globally, dementia affects over 55 million individuals, with more than 60% of them residing in low- and middle-income countries. The number of new cases is alarming, with approximately 10 million people diagnosed every year, highlighting the urgent need for awareness, support, and research to combat this growing health crisis [2]. Dementia has far-reaching consequences, affecting not only individuals with the condition but also their caregivers, families, and society. Family caregivers of people with dementia experience significant emotional distress, including anxiety, depression, and feelings of burden. It has also been estimated that family caregivers incur an average of $10,000 per year in out-of-pocket expenses, including costs related to caregiving, medical expenses, and lost income [3].

### Atrial Fibrillation and Its Epidemiology

Atrial fibrillation (AF) is the most common and clinically significant cardiac rhythm disorder that has reached epidemic proportions in the 21st century [4]. Atrial fibrillation (AF) occurs when the heart's normal rhythm is disrupted by erratic electrical signals emanating from the atria, overpowering the heart's natural pacemaker and leading to an irregular and uncontrolled heartbeat [5]. As the most common type of arrhythmia, AF poses a substantial threat to public health, leading to increased morbidity, mortality, and a considerable strain on the healthcare system. Early detection and timely intervention are crucial in preventing AF-related complications and mitigating its burden on healthcare resources [6]. The Global Burden of Disease (GBD) 2019 study demonstrated that more than 59 million individuals lived with AF in 2019 [7]. In 2021, AF was mentioned on 232,030 death certificates and was the underlying cause of death in 28,037 of those deaths [8]. The prevalence of atrial fibrillation is expected to rise significantly, affecting 6-12 million people in the US by 2050 and 17.9 million in Europe by 2060, thereby increasing the risk of ischemic stroke, a major complication of this condition [9].

### Risk Factors and Complications:

The likelihood of developing atrial fibrillation (AF) grows with age, and is further exacerbated by high blood pressure, which also becomes more prevalent with advancing age, contributing to approximately 20% of AF cases [10].




**Picture 1:** Prevalence of atrial fibrillation/atrial flutter. Legend. North America is marked in blue, Latin America and Caribbean in dark green, Europe and Central Asia in red, Middle East and North Africa in brown, Sub-Saharan Africa region in light green, South Asia in yellow, East Asia and Pacific in purple.

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Additional risk factors for AF include: [11].

- Advancing age
- High blood pressure
- Obesity
- European ancestry
- Diabetes
- Hyperthyroidism
- Chronic kidney disease
- Excessive alcohol consumption
- Smoking
- Left-sided heart chamber enlargement

The most critical complication of Atrial fibrillation is 'Stroke', which can lead to significant morbidity and mortality. Another complication includes 'Heart Failure and Heart diseases. Thromboembolism is another major complication which usually involves the brain site and other parts of body [12].

### Type 2 Diabetes and Its Epidemiology:

Type 2 Diabetes (T2D) is a significant global health concern, characterized by elevated blood glucose levels resulting from inadequate insulin production by the pancreas. Research suggests that hyperglycemia (High glucose level ) in diabetes impairs the immune response, rendering it unable to effectively combat invading pathogens and leading to increased susceptibility to infections in individuals with the condition [13]. The global diabetes epidemic has worsened significantly over the past few decades, with the number of people affected soaring from 108 million in 1980 to 422 million in 2014. Notably, the prevalence of diabetes has increased at a faster rate in low- and middle-income countries compared to high-income countries. Furthermore, between 2000 and 2019, diabetes mortality rates rose by 3% when adjusted for age. In 2019 alone, diabetes and related kidney disease claimed an estimated 2 million lives, highlighting the urgent need for effective prevention and management strategies [14]. More than 95% of people with Diabetes have Type 2 Diabetes. Individuals with diabetes are at an increased risk of developing serious health complications, including heart attack, stroke, and kidney failure. Additionally, diabetes can cause irreversible vision loss by damaging the blood vessels in the eyes. Furthermore, many people with diabetes experience foot problems due to nerve damage and poor circulation, leading to foot ulcers and potentially even amputation. These complications highlight the importance of effective diabetes management and regular monitoring to prevent or delay the onset of these issues [15].

### Purpose of the Review

The purpose of this review is to examine the association between new-onset atrial fibrillation and dementia in patients with type 2 diabetes, a group who is already at increased risk for atrial fibrillation [16]. Type 2 diabetes is an established risk factor for dementia, with a 53-73% higher risk of developing Alzheimer's disease [17]. Another study analyzed data from 9,832 type 2 diabetes patients across 13 countries, finding that over 30% had pre-existing cardiovascular diseases, underscoring the importance of investigating the atrial fibrillation-dementia link in this population [18].

## Atrial Fibrillation and Dementia

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder, and emerging evidence suggests it may contribute to cognitive decline, potentially leading to dementia [19]. Notably, AF is responsible for 20-30% of ischemic strokes, a primary cause of dementia [20]. Recent meta-analyses have solidified this link, with a 2019 analysis of 16 studies (2,415,356 participants) finding a significant association between AF and dementia risk, which strengthened with longer follow-up durations [21]. A more recent 2022 meta-analysis of 15 studies (2.8 million participants) revealed a 39% increased risk of cognitive decline in individuals with AF, further supporting the predictive role of AF in cognitive deterioration [22].

### Stroke as a cause of AF

Research has identified a link between abnormal autonomic nervous system function and atrial fibrillation (AF), suggesting that central nervous system damage, such as from a stroke, may contribute to AF development [23]. One proposed mechanism for stroke in AF is that impaired atrial contraction leads to disorganized heart cell activity, causing blood stagnation and increased thromboembolism risk [24]. Furthermore, conditions that increase AF risk, like hypertension, diabetes, heart failure, dyslipidemia, coronary heart disease, sleep apnea, smoking, and obesity, also raise stroke risk [25]. Studies have also shown that stroke patients with AF tend to experience more severe strokes and higher mortality rates compared to those without AF [26].

### Inflammation as a Risk Factor For both the AF and Dementia

Atrial fibrillation (AF) and dementia share a common link with inflammation, which appears to be both a cause and consequence of AF. Inflammation can lead to cardiac remodeling, increasing the risk of AF, while AF itself can trigger inflammation through thromboembolic events and endothelial injury. Elevated levels of C-reactive protein (CRP) and IL-6, inflammatory markers, are associated with AF development, persistence, and worse outcomes [27]. Similarly, inflammation plays a role in dementia, with

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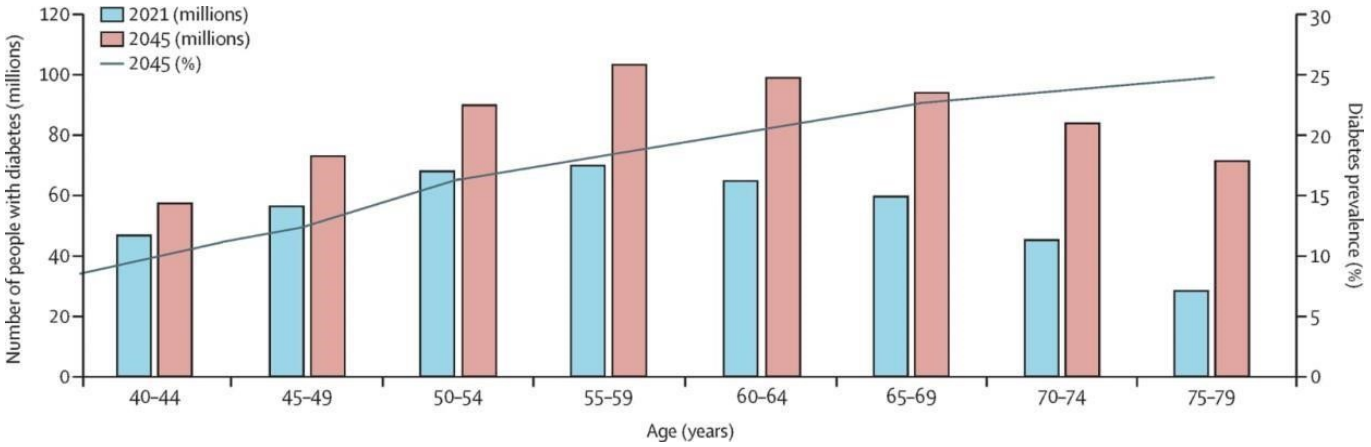
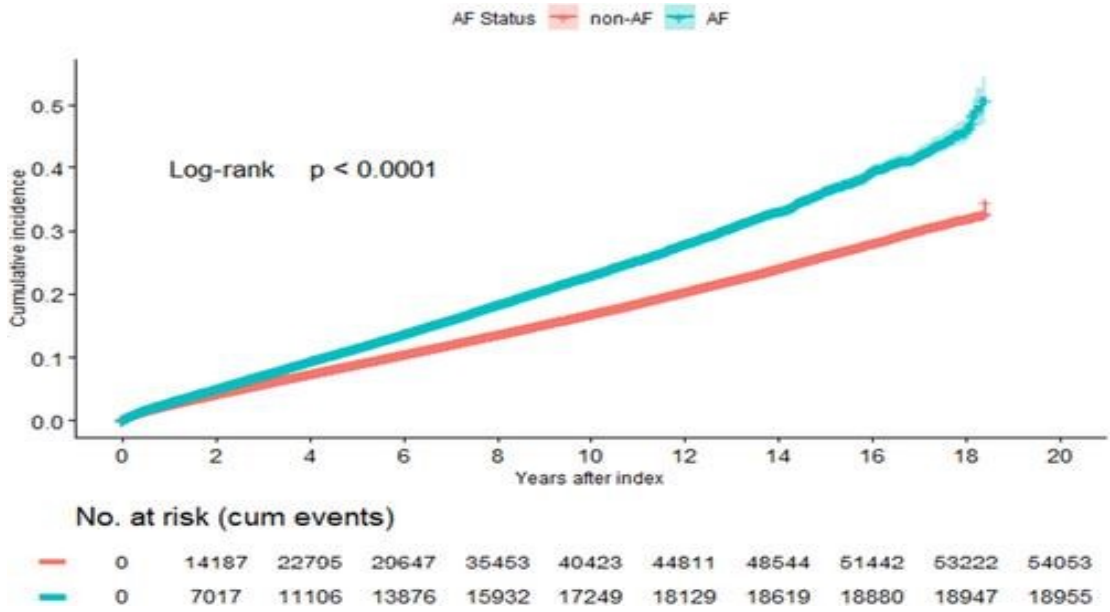



**Picture 2:** Number of people with Diabetes by age group in 2021and estimated prevalence across age group by 2045




**Picture 3:** High hazard rate of dementia in those with AF vs those who are non-AF

amyloid-β activating microglia and astrocytes, leading to neurodegeneration. CRP levels are also linked to an increased risk of dementia. The hypothesis suggests that peripheral dysregulation of cytokines and chemokines contributes to Alzheimer's disease (AD) development, and chronic conditions like AF, characterized by increased systemic inflammation, may play a role [28].

## Effect of AF on Cerebral Hemodynamics:

Atrial fibrillation (AF) may alter deep cerebral hemodynamics, particularly in lenticulostriate arteries (LSAs), which supply blood to basal ganglia and are linked to silent strokes and cerebral small vessel diseases – key drivers of dementia. A study was conducted that uses computational fluid dynamics and 7T MRI to investigate AF's effects on LSA hemodynamics [29].

Key findings: [30]

- AF reduces wall shear stress and flow velocity fields in LSAs.
- Higher heart rates in AF increase the risk of atheromatosis and thrombogenesis in LSAs.
- Cerebral perfusion and hypoperfusion events depend on Circle of Willis geometry and AF-induced stochastic heart rates [31].

However, there is growing evidence that Atrial fibrillation (AF) may increase the risk of vascular dementia and cognitive impairment by altering deep cerebral hemodynamics, even without clinical strokes [32].

## Type 2 Diabetes (T2D) and Dementia

Type 2 diabetes poses a growing global health concern,

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disproportionately affecting the elderly population. Research consistently shows that type 2 diabetes increases the risk of developing dementia [33], including Alzheimer's disease and vascular dementia. The underlying mechanisms, as revealed by pre-clinical studies, involve:

1. Neuronal insulin resistance
2. Impaired insulin signaling
3. Chronic inflammation
4. Mitochondrial dysfunction
5. Vascular damage

These factors contribute to the accumulation of harmful proteins like β-amyloid, tau, and GSK3β, ultimately leading to an earlier onset of dementia in individuals with impaired glucose metabolism [34].

## Type 3 Diabetes (T3D) and Alzheimer's Disease

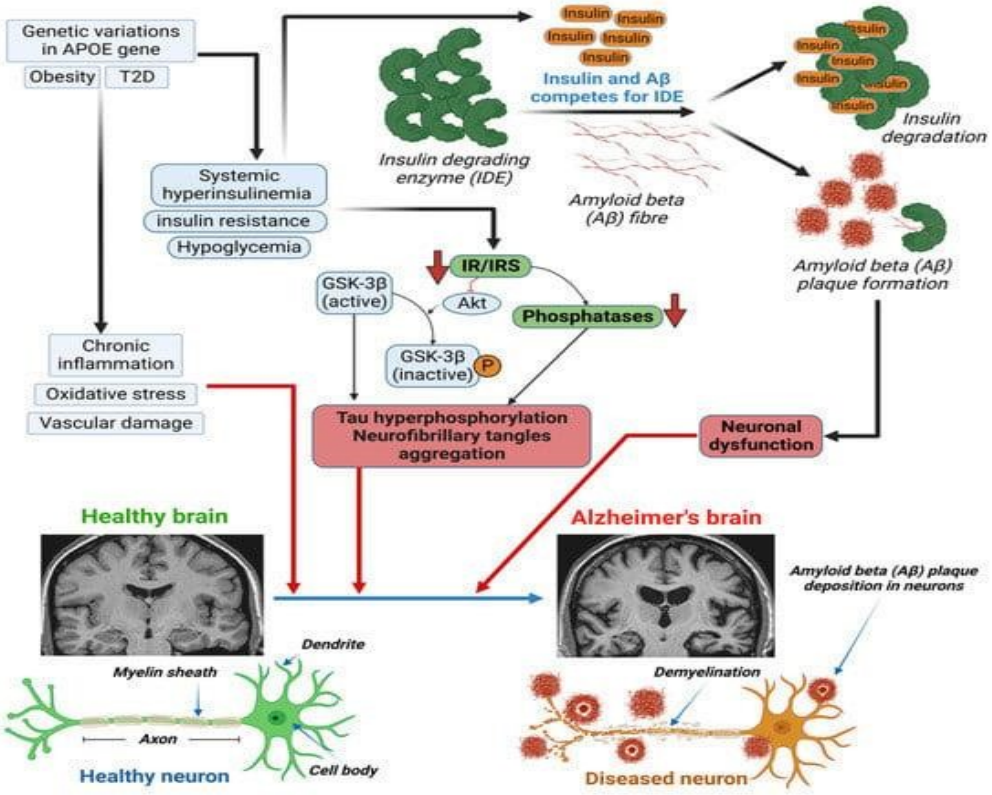
The link between Alzheimer's disease (AD) and type 2 diabetes remains unclear, but research suggests that uncontrolled blood sugar levels may increase the risk of developing AD. This connection suggests the co-occurrence of Type 2 Diabetes Mellitus (T2DM) and neurodegenerative diabetes, termed T3DM or "neuroendocrine diabetes" [35]. T3D is characterized by insulin resistance in the brain, which can significantly impact cognitive function and contribute to the development of AD [36]. Recent studies continue to support the association between T3D and AD, highlighting the role of impaired insulin signaling in: [37].

1. Amyloid-β precursor protein toxicity
2. Amyloid-β clearance

It has also been suggested that glucose homeostasis plays a crucial role in the development of Type 3 Diabetes Mellitus (T3DM). In T3DM, brain glucose uptake and metabolism are impaired, leading to a complex interplay between metabolic and neurodegenerative processes. [38].

## Brain: An Insulin Sensitive Organ

Insulin resistance, a pervasive metabolic dysfunction often entwined with obesity, severely impairs the brain's ability to respond to insulin, leading to a devastating decline in insulin sensitivity [39]. This crippling effect can be attributed to two primary mechanisms: a diminished responsiveness of brain cells to insulin signals, or a reduced permeability of the blood-brain barrier, hindering insulin's entry into the brain [40]. Consequently, insulin resistance unleashes a cascade of neurochemical disruptions, including a precipitous drop in acetylcholine levels, a vital neurotransmitter that plays a critical role in cognitive function [41]. This intricate relationship underscores the profound impact of insulin resistance on the development and progression of Alzheimer's disease, highlighting the urgent need for effective management and therapeutic strategies [42].




**Picture 4**: Mechanism of altered insulin levels/signaling in developing Alzheimer's diseases (AD) in diabetes.

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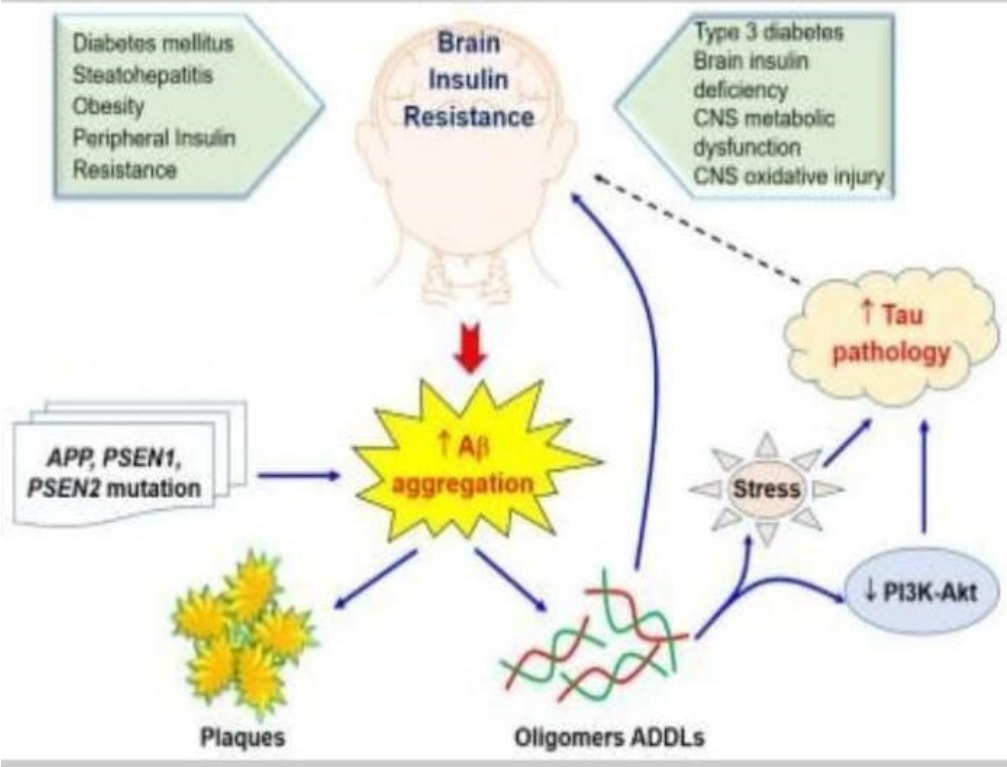
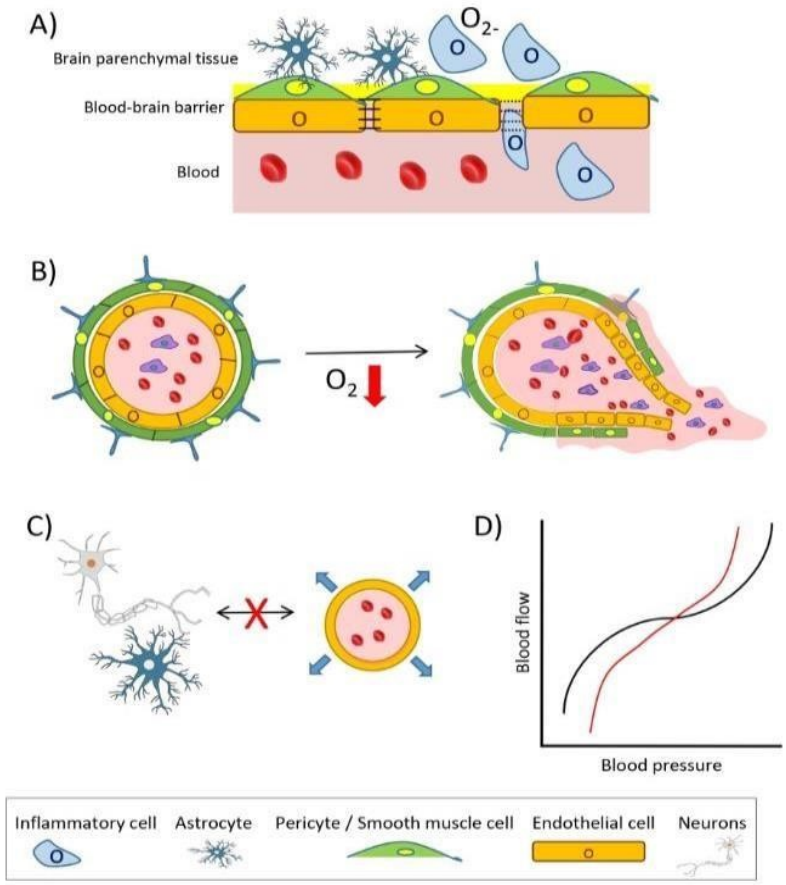



**Picture 5:** Insulin resistance and its effect on Brain function




**Picture 6:** Detrimental effects of Cerebral Microvascular Dysfunction

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### Hyperglycemia and Neuronal Damage

A toxic triangle of hyperglycemia, oxidative stress, and Inflammation drives the development and progression of type 2 diabetes mellitus [43]. When blood sugar levels rise beyond levels, the delicate balance of vascular physiology is disrupted, plunging the endothelium into dysfunction [44]. This, in turn, unleashes a surge in ROS generation which triggers a cascade of gene dysregulation, including the aberrant expression of inflammatory cytokines and adhesion molecules [45]. Chronic, low-grade inflammation is a known precursor to type 2 diabetes, with subclinical inflammation contributing to insulin resistance and metabolic syndrome. Thus, oxidative stress and inflammation engage in a vicious cycle, each fueling the other's production [46]. The consequences of chronic hyperglycemia are far-reaching, with toxic effects on neurons, leading to the formation of advanced glycation end products, oxidative damage, and neuronal injury. Inflammation and dyslipidemia join forces to wreak havoc on neuronal health, culminating in cognitive impairment. This complex interplay underscores the urgent need for effective management of hyperglycemia and its associated complications [47].

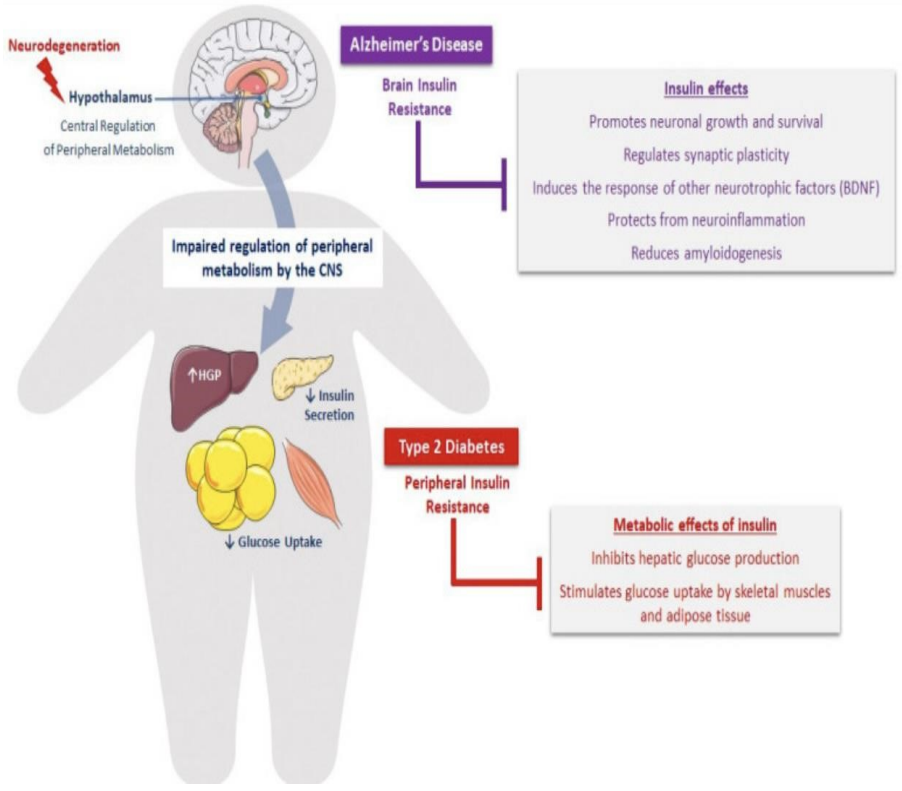
### Microvascular Dysfunction in Diabetes:

Diabetes-related microvascular dysfunction has far-reaching consequences for brain health, leading to Cerebral Small Vascular Diseases (CSVD). This, in turn, significantly increases the risk of cognitive decline, dementia, and Alzheimer's disease. Even prediabetes has been linked to a higher risk of dementia and Alzheimer's. The impact of CSVD on individuals with diabetes extends beyond cognitive impairment, manifesting as [48]:

- Gait disturbances, such as a slower pace and difficulty with multitasking
- Mood disorders, including apathy and depression, which are twice as prevalent as in the general population
- A heightened risk of developing Parkinson's disease, as reported in multiple metanalyses

## The Interplay of Af, T2d And Dementia:

Type 2 diabetes mellitus (T2D) is linked to cognitive decline and a heightened risk of dementia, especially in the context of significant cerebrovascular events. [49] Additionally, patients with atrial fibrillation (AF) who have diabetes may face an increased risk of developing vascular dementia.[50]Although Type 2 Diabetes (T2D) and Alzheimer's Disease (AD) were initially thought to be unrelated, substantial epidemiological evidence now indicates that diabetic patients have a higher risk of developing AD. Furthermore, there is significant experimental evidence suggesting a shared pathophysiological mechanism between the two diseases. Anatomical and functional abnormalities are observed in the same brain regions affected by both T2D and AD. [51]




**Picture 7**: Type 2 Diabetes and its association with dementia.

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Type 2 Diabetes Mellitus (T2DM) has been strongly linked to an increased risk of developing atrial fibrillation (AF), and is recognized as an independent risk factor for the condition. Atrial fibrillation (AF) primarily leads to atrial enlargement and fibrosis. Since myocardial fibrosis is independently linked to type 2 diabetes mellitus (T2DM), individuals with diabetes have a significant underlying condition that increases their risk of developing AF. [52] Type 2 diabetes mellitus (T2DM) exacerbates mitochondrial stress and contractile dysfunction in the atria. Specifically, patients with both T2DM and atrial fibrillation (AF) exhibit more pronounced changes in mitochondrial oxidative phosphorylation (OXPHOS), complex assembly, and oxidation compared to those with AF alone [53].

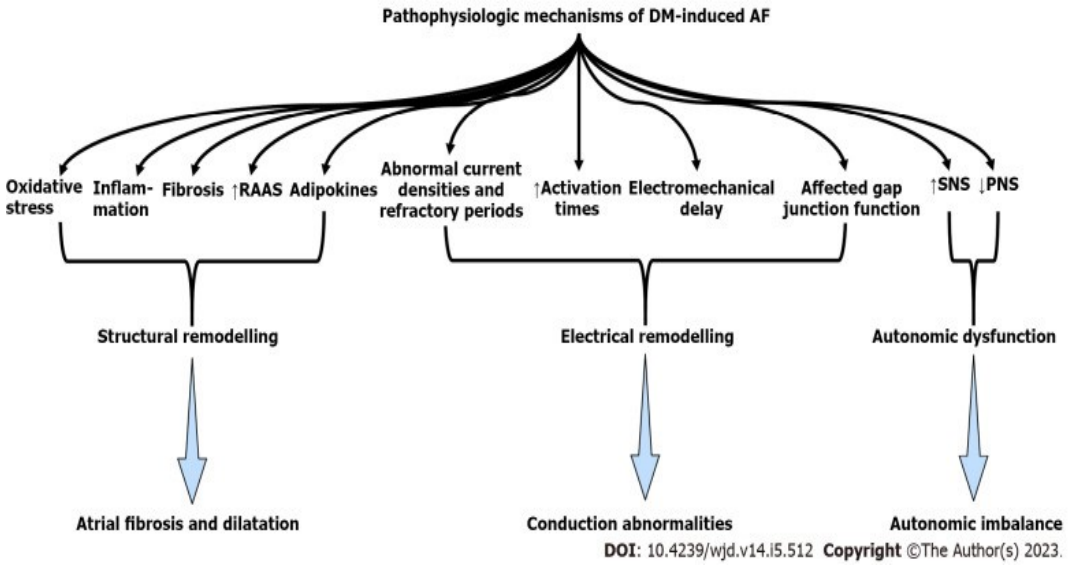
Microembolization and reduced blood flow associated with atrial fibrillation (AF) may trigger ischemic demyelination akin to what is observed in cerebral small vessel disease (CSVD), potentially exacerbating cognitive decline.[54]

Both atrial fibrillation (AF) and dementia are associated with a proinflammatory state. Inflammation seems to play a dual role, acting both as a cause and a consequence of AF.[55] Inflammation increases hypercoagulability and promotes thrombus formation, heightening the risk of stroke and impairing cerebrovascular regulation. This dysfunction has been associated with Alzheimer's disease and vascular dementia.[56] Unveiled cerebrovascular dysfunction, driven by hemodynamic, oxidative, and inflammatory mechanisms, is a likely explanation for sudden cognitive changes observed with the onset of atrial fibrillation (AF) [57].

## Clinical Implications

Given the rising rates of diabetes mellitus and atrial fibrillation worldwide, which are significant risk factors for stroke and cardiovascular mortality due to thromboembolic risk, early prevention and screening are crucial. Screening for atrial fibrillation before symptoms appear is particularly important for certain patient populations. Clinicians should consider routine screening through pulse palpation or ECG rhythm strips in elderly individuals with type 2 diabetes and those with renal complications. This approach may facilitate the early initiation of effective therapy.[58] While there are common risk factors for both atrial fibrillation (AF) and dementia, AF on its own is a predictor of cognitive decline and the development of dementia. The risk of cognitive issues associated with AF increases with older age, as well as with conditions such as hypertension, dyslipidemia, depression, smoking, diabetes, and a history of stroke.[59]

Certain studies suggest that to more accurately determine the connection between atrial fibrillation (AF) and dementia, it is advisable to evaluate biological biomarkers (from cerebrospinal fluid or plasma) alongside brain imaging and cognitive impairment tests in individuals with AF. Identifying specific biomarkers that predict cognitive decline in AF patients could enhance screening and management strategies, and these biomarkers may also be useful for risk stratification in patients who are considered clinically low risk.[60] Hypertension, or high blood pressure (BP), is a key factor that greatly increases the risk of developing dementia. [61] Managing hypertension starting in middle age may help delay the onset of dementia in older adults [62]. Obesity plays a major role in the development of dementia. Promoting healthy eating habits and encouraging physical activity, particularly in at-risk groups, are essential for preventing and managing obesity [63]. Individuals with diabetes can benefit from adopting a healthy diet and exercise routine, with the Mediterranean diet currently being recommended. Strategies aimed at preventing the onset of diabetes may be the most effective approach for modifying risk.[64]




**Picture 8**: Pathophysiologic mechanism showing diabetes-induced atrial fibrillation.

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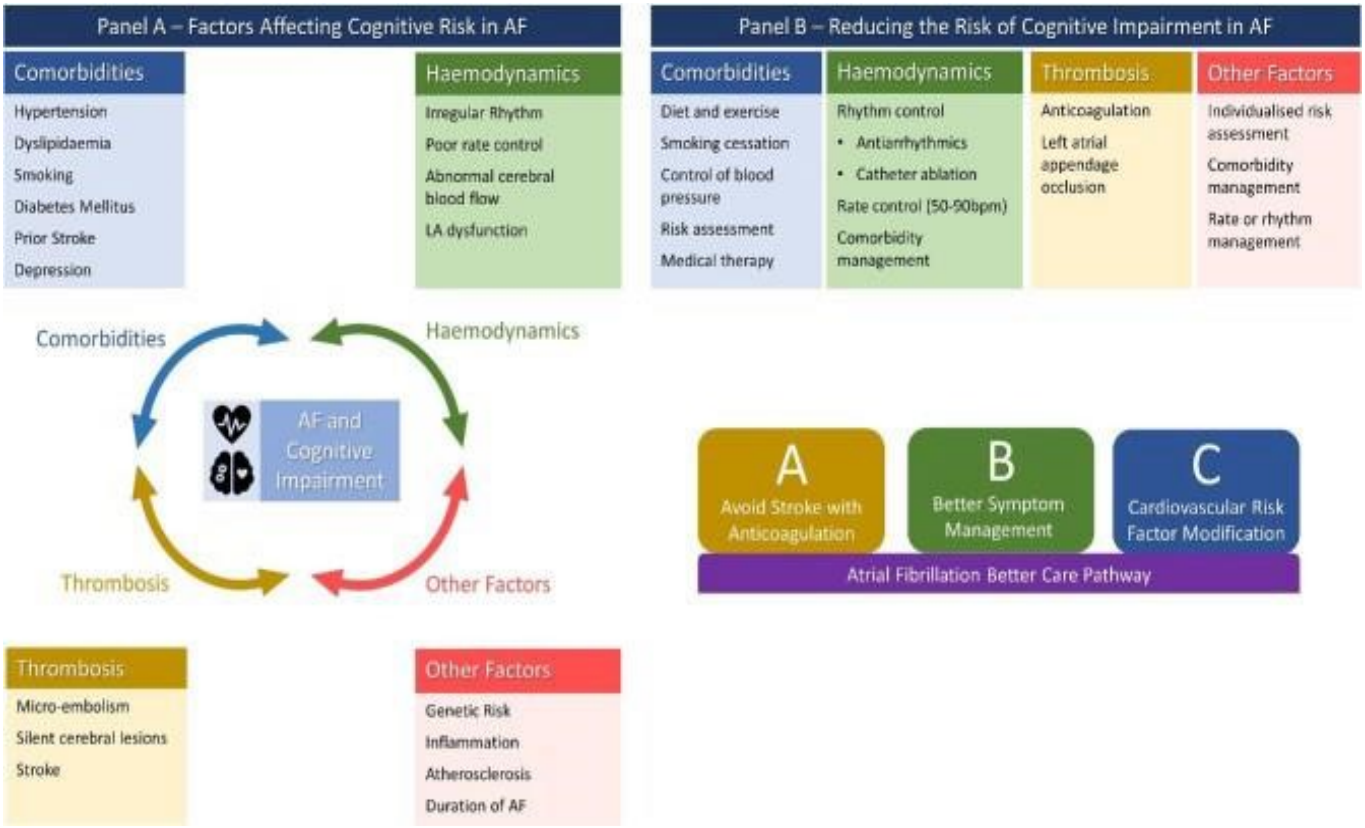


**Picture 9:** Risk Factors for Cognitive Decline in Atrial Fibrillation and Their Management

Cardiovascular risk factors are key predictors of dementia in later life. Since lipid fractions are easily measurable and can be managed through diet, exercise, and cholesterol-lowering medications (CLDs), their association with the development of dementia is particularly significant, representing a potentially modifiable risk factor.[65] The impact of stroke is substantially higher in individuals with Type 2 Diabetes (T2D) compared to those without it. Stroke often leads to a decreased quality of life and places a considerable strain on health resources.[66] In patients with atrial fibrillation (AF), the clustering of unhealthy behaviors—such as inadequate exercise, regular smoking, and frequent alcohol consumption—elevates the risk of major adverse cardiovascular events, including ischemic stroke. Conversely, adopting healthy lifestyle habits is linked to a significant reduction in the risk of ischemic stroke.[67]

Previous studies have shown that adopting a healthy lifestyle—such as avoiding smoking, consuming alcohol in moderation, following a balanced diet, maintaining a healthy weight, and getting adequate sleep—can reduce or delay the risk of stroke.[68]

## Future Directions

Conducting large-scale, prospective studies with long-term follow-up is crucial to comprehensively understand the relationship between atrial fibrillation (AF), type 2 diabetes (T2D), and dementia. These studies allow researchers to accurately quantify the combined risk of AF and T2D on dementia incidence and progression over time. T2D is characterized by insulin resistance, which can lead to impaired glucose metabolism in the brain. This may exacerbate neurodegenerative processes, thereby amplifying the impact of AF on dementia risk. Advanced age is a significant risk factor for dementia, and elderly patients with T2D and AF are likely at higher risk due to age-related brain changes and cumulative vascular damage. Understanding the molecular mechanisms that link T2D to AD to establish common preventive and ultimately curative measures to delay the onset and restrain the progression of these two pathologies is a major research challenge [69]. Prevention of marked hyperglycemia with appropriate adjustments of glycemic management should be tailored to suit the individual requirements of the patient periodically to achieve this goal [70].

## Conclusion

Outlook Atrial fibrillation, diabetes, and dementia a tangled threesome This review focuses on the intricate- alarms me at times even, the relationship between atrial fibrillation (AF), type 2 tugs cardiac pacemakersT2D) as well dementias. Usually, if any one of these three conditions are developed the other two will coexist and each disorder increases the

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risk for another gehört. These connections originate from a common soil of risk factors such as inflammation, vascular dysfunction and oxidative stress that are instrumental for the development of pathological processes in both brain areas in neurodegeneration and cardiovascular damage. Understanding the relationships between AF, T2D and dementia are important for clinical management. Defined methods for tracking a biotic agent could be critical in monitoring those most at risk, especially with comorbidities. As always, early detection and intervention are critical to prevent these conditions from becoming more severe or of life-threatening consequences.

A collaborative, multidisciplinary approach is required to manage the complex needs of those with AF + T2D and dementia. Cardiologists, endocrinologists, neurologists and other healthcare professionals need to come together in treating the two conditions as imperative that each case be managed holistically rather than in isolation. Solutions to such complex problems require a more holistic approach and treatment programs should be individually tailored using combined risk factor reduction, lifestyle intervention alongside pharmacological therapy. These findings are particularly problematic because the concurrence of AF, T2D and dementia is difficult to manage clinically; however, research efforts continue to advance our understanding about how best treat these diseases. This exploration of common mechanisms behind these conditions can help us in the search for targeted interventions that might break this vicious cycle and provide relief to patients afflicted by one or more of both diseases.

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