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# Metabolic Syndrome and Its Biomarkers in the Development and Progression of Alzheimer's Disease and Other Dementias

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## Abstract

Metabolic syndrome is a condition that includes several components which, individually and together, are steadily increasing in prevalence worldwide. These include obesity, dyslipidemia, hyperglycemia, and hypertension. On the other hand, Alzheimer's disease, one of the family of dementias, is considered a disease of the elderly, whose numbers are also increasing. However, it has been found that the presence of the components of metabolic syndrome in earlier life, especially middle age, increases the risk of Alzheimer's disease, although it has recently been suggested that these components may begin the progression to dementia as early as adolescence. The full pathophysiology of Alzheimer's and the mechanisms by which metabolic syndrome affects it are not fully understood to date. The present chapter examines the association between metabolic syndrome and Alzheimer's disease and the association between the components of metabolic syndrome and Alzheimer's. The authors also represent the genetic involvement in this association, since various genes have been found to be common to both disorders.

**Keywords:** metabolic syndrome, Alzheimer's disease, biomarkers

## 1. Introduction

Metabolic syndrome is a medical condition that includes obesity, dyslipidemia, hyperglycemia, and hypertension. It and its components have been recognized as an important risk factor for cardiovascular disease, both macrovascular and microvascular. Given the worldwide epidemic in obesity and diabetes, this syndrome has received serious attention in recent years, although the condition has been studied since it was first described by G. Reaven in 1988 [1]. Metabolic syndrome has been linked to the risk of cardiovascular disease (CVD) and, more recently, to neurodegenerative diseases, including cognitive decline and dementia, which include Alzheimer's disease (AD) [2–4]. The complex relation between metabolic syndrome and dementia is not well understood and remains elusive and controversial. Differences in age, definitions, and sample size have further obscured the truth.

Just what is Alzheimer's disease? Alzheimer's disease is considered a chronic neurodegenerative illness affecting the cerebral cortex and hippocampus that lasts 8–10 years but which has a preclinical period of 20–30 years. AD is a growing health

concern, given the increase in elderly worldwide. Surprisingly, this disease can recede in individuals over 98 years of age [5]. Currently, it is estimated that 1 in 9 adults in US suffers from this disease, and that number is expected to grow by 40% by 2025 [6, 7]. AD is characterized by two factors: neuron plaques made up of amyloid beta ( $A\beta$ ) protein and phosphorylated tau protein, which forms altered structures and leads to intercellular neurofibrillary tangles. Amyloid- $\beta$  oligomers have been shown to cause tau phosphorylation in vitro, which would lead to neurodegeneration. In addition, it has been suggested that amyloid- $\beta$  also induces tau pathology in vivo [8]. This infers that the amyloid- $\beta$  lesions precede the tau phosphorylation. Amyloid- $\beta$  is found in the mitochondrial membrane. Abnormalities in amyloid- $\beta$  cause an increase in the production of reactive oxygen species (ROS), leading to oxidative stress and lipid peroxidation in the neurons. This oxidative stress reduces levels of superoxide dismutase in the mitochondria. This alteration, in turn, leads to an increase in hyperphosphorylation of tau. RCAN1 is a protein produced in response to oxidative stress. If RCAN1 is chronically stimulated, may promote neurodegeneration [9].

The pathology of Alzheimer's disease, and various other dementias, includes loss of neuronal connections in the hippocampus and temporal lobes, neurofibrillary tangles (NFTs), amyloid- $\beta$  ( $A\beta$ ), and amyloidopathy of the cerebrovasculature [10].

While the exact mechanisms are still not entirely clear, it has been noted that other conditions usually accompany AD, such as cardiovascular disease and metabolic syndrome. In addition, Alzheimer's usually includes various important comorbidities, including white matter lesions; brain hypoperfusion, usually undetected microinfarcts; and cardiovascular dysfunction. Other comorbidities include obesity, diabetes, and hypertension, collectively known as metabolic syndrome [11, 12].

However, the definitions of Alzheimer's disease and other forms of dementia are slowly becoming blurred, which may suggest that dementia, and Alzheimer's disease in particular, is the result of a series of various pathologies which all converge [13]. Results from the Nun Study and Honolulu-Asia Aging Study indicate that a complex set of cerebral alterations determines the progression of clinically diagnosed AD [14]. The complete mechanisms for the progression of dementia are not yet known. Neither is how the components of metabolic syndrome individually and collectively trigger cognitive decline. However, research is currently focusing on various aspects of this association, in order to design better strategies to combat both conditions.

In addition, various genetic factors have been uncovered which are common to both diseases, suggesting an association [15].

The present chapter will look at the effect of the metabolic syndrome, and each of its components, on the presence and progression of Alzheimer's disease and other related dementias. It will also look at the genetic factors which have been suggested as being associated, as they are common to both conditions. The authors will briefly review the association of age to the progression to Alzheimer's disease.

## **2. Metabolic syndrome and Alzheimer's disease**

The twenty-first century has seen a surge of interest in the association between metabolic syndrome and dementia, specifically, Alzheimer's disease. Given the epidemic of metabolic syndrome and its components (obesity, diabetes, hypertension) worldwide, and the fact that populations are living longer and therefore more prone to age-related diseases, this is not surprising. There is mounting evidence that the presence of metabolic syndrome, or of its components, increases the risk of AD. Although the exact physiopathology of AD is not completely understood, various studies have discovered links between these two conditions.

In the North Manhattan study, each of the components of metabolic syndrome was measured for the risk of dementia. Elevated levels of pro-inflammatory cytokines, including tumor necrosis factor (TNF) was associated with the risk of dementia, as were HDL-cholesterol and the presence of diabetes, although in univariate analysis high blood pressure also associated. This study suggested that metabolic syndrome be considered as a risk factor as a whole, even when the individual components did not significantly increase the risk [16]. Various studies have stated that the greater the number of components of metabolic syndrome present, the greater the risk of dementia [16, 17].

Some studies have found that metabolic syndrome is a risk factor for dementia up to a certain age (reports vary from 65 to 80 years as the cutoff point), and then it becomes a protector. However, Fan et al. found that the onset of metabolic syndrome increased the risk of dementia irregardless of the age at onset, meaning that the onset of metabolic syndrome even beyond these cutoff points poses a risk of Alzheimer's disease [18].

Another possible explanation for this enigma was presented by Watts et al., who believe that the relationship between metabolic syndrome and dementia is not linear. They believe that while the metabolic biomarkers at midlife signal the onset of Alzheimer's disease, in the elderly, they are signs and symptoms rather than causes. However, they point out that by then the prolonged effects of metabolic syndrome have already progressed over decades and the systems involved in cognitive function have been altered [19]. Bowler et al. note that, in addition, the elderly are frequently in poor health, including malnutrition, which may mask or overpower the effect of metabolic syndrome [20].

At the same time, a study among Chinese population with mild cognitive impairment found that the presence of three or more components of metabolic syndrome increased the risk of Alzheimer's disease four times and twice as great just with the presence of diabetes [21]. Likewise, a study with Italian population found that the presence of metabolic syndrome in patients with mild cognitive impairment was a predictor of Alzheimer's disease over the 3.5 years of follow-up in their study. They also noted that among the components of metabolic syndrome, hypertriglyceridemia, abdominal obesity, and hypertension were the most predictive of progression to AD [22].

## **2.1 Obesity and dementia**

Obesity has become a worldwide epidemic in recent years. Hand in hand with this growth, attention has turned to the relation between obesity, as measured by body mass index (BMI), and dementia, specifically Alzheimer's disease. Since this is one of the factors of AD that can be controlled, it is important to consider in the timely prevention of progression to dementia.

Obesity impacts dementia not only by limiting blood supply to the brain but also by increasing the number of fat cells, which restricts the white matter of the brain and causes cognitive decline. To put this in perspective, the average human has a total of 5 l of blood. More fat translates into less blood supply for the brain, causing ischemia [23]. In addition, obesity entails a higher concentration of adipokines (fat cells from cytokines). These decrease the brain's white matter, resulting in decreased neuronal connections and brain atrophy. Therefore, obesity as early as adolescence has vascular repercussions later in life, mostly due to the continued inflammation and adipose-related hormone levels [23]. In fact, the presence of obesity in middle age increases the risk for AD in later years twofold, more than hypertension or high cholesterol [24].



Finally, the underlying causes of obesity, such as a diet high in fats and sugars, influence gut microbiota and disrupt the so-called gut-brain axis, resulting in inflammation that ends in neurodegeneration and, again, brain atrophy [23].

Fibroblast growth factor 21 (FGF21) is a hormone that plays an important role in metabolic regulation and has a positive correlation with BMI and obesity. However, in the presence of neuronal dysfunction, FGF21 is released, reducing the damage caused by the neuronal activity. This mechanism is complicated by obesity, which effectively blocks the FGF21 activity, permitting cognitive decline [25].

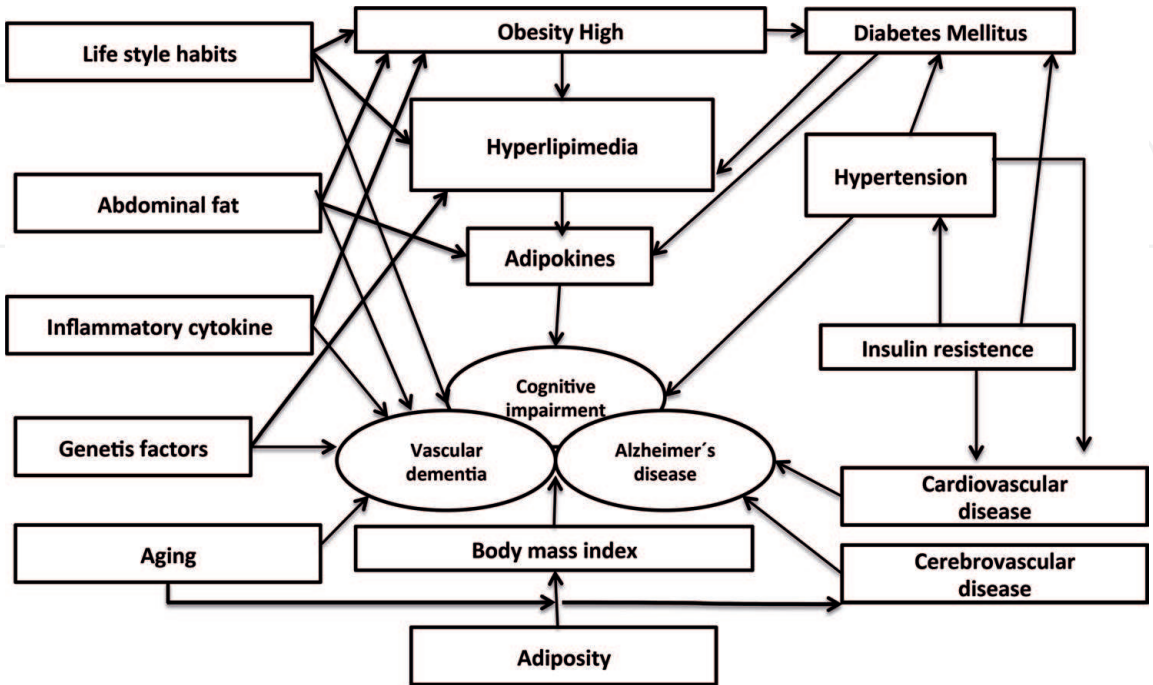
At a more direct level, obesity causes cerebral hypoperfusion, which increases  $\beta$ -amyloid production which, in turn, causes endothelial dysfunction, terminating in a dangerous cycle that results in the pathogenic changes found in dementia. This occurs due to a rise in levels of asymmetric dimethylarginine, which decreases nitrous oxide, causing oxidative stress. Various studies have shown that dysfunction of the brain mitochondria increases pro-apoptotic proteins (bax and bad) and decreases anti-apoptotic protein (Bcl-2), resulting in brain apoptosis [26].

Increased fat mass and obesity-associated protein (FTO) are responsible for the prefrontal cortex's processing of food stimuli (sight, smell, taste). If FTO is overexpressed, it leads to an increase in food consumption, resulting in obesity. FTO has also been shown to trigger the phosphorylation of tau in the neurons [27].

Given the fact that obesity is a controllable condition, this should be a focus in the prevention of AD and dementia. It should also be remembered that weight loss programs also reduce other risk factors for AD involved in metabolic syndrome, such as dyslipidemia and hypertension. **Figure 1** shows the possible link between obesity and dementia.

2.2 Dyslipidemia and dementia

It has been suggested that high low-density cholesterol (LDL-c) and low high-density cholesterol (HDL-c) as early as midlife contribute to the development of AD later in life. One study found that high total cholesterol (>240 mg/dL) as early



**Figure 1.** Possible link between obesity and dementia. Some studies suggest that several factors associated with obesity are also associated with the development of Alzheimer's disease.

as in one's 30s carries a 57% higher risk of developing AD 30 years later [28]. Low LDL-c early in life associates with A $\beta$  plaques later on, a biomarker of AD [29]. This has been proven to be true even in individuals as young as 40 years old [30].

Excess lipids can trigger an increased production of A $\beta$ , leading to the development of plaques. These lipids may also lead to insulin resistance, which will be discussed later on. In addition to the cholesterol, serum triglycerides are a vital factor in this process. Hypertriglyceridemia has been shown to affect brain processes, by altering the peptides crossing the blood-brain barrier, such as decreasing leptin bioavailability. Other affected peptides include galanin (GAL), the opioid peptides enkephalin (ENK) and dynorphin (DYN), and the orexins (ORX) [31]. One study in mice found that by lowering triglycerides, especially triolein, cognitive damage could actually be reversed [32]. The metabolism of cholesterol and lipid proteins in the central nervous system occurs independently from the peripheral nervous system. Processed cholesterol can cross the blood-brain barrier and bind to either LDL-c or HDL-c. These lipids, especially cholesterol, have a key function in the physiopathology of AD. We have seen, and will discuss further, that high cholesterol in middle age increases the risk of AD in later life. However, high levels of cholesterol later in life actually reduces the risk of AD [33].

While exact mechanisms remain elusive, it is very possible that the inflammation that accompanies dyslipidemia is at the root of this association and holds a key role in the pathogenesis of dementia. It should be noted that there are genetic implications, which will be discussed later on. It has been found that mononuclear cells of elderly AD patients have high levels of inflammatory cytokines, such as IL-1 $\beta$ , IL-6, IL-12, IL-16, and IL-18 and tissue growth factor (TGF)- $\beta$ 1. It has been found that these inflammation cytokines, as well as anti-inflammatory IL-10 and IL-13, are found in increased concentrations in the brains of AD patients [34].

In AD, A $\beta$  reaction with microglial receptors can lead to a highly inflamed state [35]. It appears that the activation of the microglial cells unleashes the pro-inflammatory cytokines, leading to increased A $\beta$  and tau hyperphosphorylation. In addition, IL-1 $\beta$  can cause the production of inflammatory factors and has shown to play a variety of roles in neuron damage.

It is widely accepted that obesity incurs systemic inflammation. Hypercholesterolemia is known to increase the levels of inflammatory cytokines. Neuroinflammation and neurodegeneration increase microglial activation. This leads to a further inflamed state, resulting in a vicious cycle. However, lifestyle changes that lower LDL-c and triglycerides and raise HDL-c can help prevent or possibly reverse the cognitive damage.

### **2.3 Diabetes and dementia**

One of the most widespread outcomes of metabolic syndrome is diabetes mellitus. Both type 2 diabetes mellitus (T2DM) and dementia are considered age-related diseases, although, as we will see later on, this assumption may need to be changed. While the full impact of diabetes on cognitive decline and dementia is still not completely known, alterations in cognition begin as early as pre-diabetes [36]. Various domains of the brain have been shown to be affected by T2DM, suggesting that the diabetes negatively impacts the processing networks [37]. However, diabetes has not been directly linked to the neuropathology of dementia. Nevertheless, there are other means by which diabetes may be closely linked to dementia, especially Alzheimer's disease. One of these links may lie in the fact that T2DM usually leads to atherosclerosis, which mediates cognitive decline. Another may lie in the alterations to cerebral glucose metabolism, as suggested by Chornenkyy et al.

[38]. Evidence from studies such as the Baltimore Longitudinal Study of Aging have shown, through autopsy, that glucose metabolism is altered in the orbital and prefrontal cortex, temporal cortex (middle gyrus, parahippocampal gyrus, and uncus), and cerebellar regions in cases of Alzheimer's disease [39, 40]. It is possible that there is an upstream effect and that these alterations in glucose metabolism impact the  $\beta$ -amyloid deposition, a characteristic of AD. In addition, these alterations in glucose metabolism would affect the mitochondria, causing them to release reactive oxygen species (ROS) and triggering apoptosis. The increased ROS, in turn, accelerates the metabolic syndrome while at the same time impacting  $\beta$ -amyloid processing.

Another means by which T2DM may affect AD lies in lipid metabolism. Cholesterol affects the peptide levels in  $\beta$ -amyloids. Increases in cholesterol cause increases in the levels of cholesteryl esters, which in turn increase  $\beta$ -amyloid concentrations [41].

Insulin resistance (IR) is one of the main characteristics of T2DM. Research has increasingly found that IR is a factor in dementia. Much attention is being paid to the inflammatory markers associated with IR, such as interleukin-6 (IL-6) and C-reactive protein (CRP). In fact, Singh-Manoux et al. found that increased IL-6 as early as middle age is a predictor of dementia later in life [42]. It has been suggested that these inflammatory cytokines cause thrombotic vascular events, which then lead to cerebral infarction. Another way in which IR may affect dementia is related to the higher cortisol levels found in T2DM, which have long been linked to cognitive decline and dementia.

Finally, one of the common complications of T2DM is diabetic autonomic neuropathy (DAN). It has been suggested that the presence of DAN signals alterations in the hypothalamus, midbrain, brainstem and cortex. One study found that treatment with plasmapheresis improved performance on cognitive tests, indicating improvement in autonomic neuropathy [43].

## **2.4 Hypertension and dementia**

Hypertension has been identified as a risk factor for cognitive decline. In fact, various studies have associated midlife hypertension with dementia later in life [44, 45].

Left ventricular hypertrophy (LVH) is usually an end result of hypertension. A very recent study has associated the presence of LVH in midlife with the incidence of dementia [46].

It is known that unchecked hypertension leads to microinfarcts and microhemorrhages, which in turn inhibit cognitive function. Hypertension also induces an increase in A $\beta$  peptides in the brain while inhibiting vascular clearance of amyloids [47]. The ensuing accumulation results in amyloid angiopathy, a classic indicator of AD. In addition, these microinfarcts and microhemorrhages cause white matter lesions. A study in 2004 found that patients with hypertension and the resulting white matter lesions did significantly poorer on neurological tests [48]. Unfortunately, this study did not include adequate follow-up to track progression to dementia and Alzheimer's disease.

One important recent study concentrated not on amyloid activity but rather on tau phosphorylation. Raz et al. [49] found that the vascular alterations caused by hypertension promoted tau phosphorylation, leading to cell death and brain atrophy. They explain that chronic hypertension alters the arterial endothelial cell lining, causing hypoxia and changing oxidative metabolism. This in turn triggers an inflammatory cascade that ends in neuronal cell death. The hypoxic hypoperfusion also triggers a neuropathological cycle, which involves the production of free



radicals, activation of microglia, alteration of the blood-brain barrier, and tau hyperphosphorylation.

Several studies have found that the use of antihypertensive drugs, especially diuretics, can reduce the risk of Alzheimer's disease. These studies include the Ginkgo Evaluation of Memory study (GEM) [50] and the Cache County study, a hallmark of study in this area [51, 52]. More research is needed to see if the use of antihypertensive medication and/or diuretics is a therapeutic option for those with a high risk of Alzheimer's.

### **3. Genetics, metabolic syndrome, and dementia**

With the development of genome-wide association studies (GWAS), more information about the association between metabolic syndrome and dementia has become available. By comparing the phenotypes associated with cardiovascular disease and metabolic syndrome with those most common to Alzheimer's disease, researchers have been able to establish common links, and with that information establish the genetic risk factors for metabolic syndrome that also confer risk of Alzheimer's disease [53].

Apolipoprotein E (ApoE) is the major cholesterol transporter in the brain. With the discovery of the ApoE4 allele, a key to the pathogenesis of AD was uncovered. It was found that the presence of this allele associates with the risk of developing AD at a younger age, especially in the presence of ApoE4/E4 homozygotes [54].

However, ApoE2/E3 has a protector effect. In addition, some ApoE4- haplotypes enable the protector effect of lipids on neural membranes, while ApoE4+ impairs this effect [55]. This may help at least to partially explain the difficulty in assigning the role of lipids in AD. Nevertheless, single nucleotide polymorphisms (SNPs) of ApoE have been identified as being related with lipid metabolism (CLU and ABCA7) and with inflammation (CR1 and HLADRB5) [56, 57]. Nevertheless, this situation may not be a permanent one. A case study published by Brown et al. intervened in the case of a 38-year-old man with metabolic syndrome and mild cognitive decline, who came from a family with a background of Alzheimer's disease. He was put on a ketogenic diet and given a program of high-intensity exercise. After 10 weeks, the biomarkers of the metabolic syndrome improved, as did his memory function. Insulin signaling approached normal, indicating that the ApoE4 gene had been effectively silenced [58].

These are not the only genetic markers. A rare variant in TREM-2 shares in the risk of AD [59, 60]. Reduce of the biomarkers of metabolic syndrome showed marked improvement, and his memory improved; expression of SORL1 also leads to A $\beta$  accumulation. In addition, the interaction between SORL1 and ApoE closely associates with an increased risk of AD [61]. Another candidate is sirtuin 1 (SIRT1). It has been suggested that the protein of this gene, together with PGC1 $\alpha$ , may help maintain brain function by participating in the regulation of mitochondrial function. This, in turn, activates the endothelial growth factor (VEGF) and conserves the integrity of the blood-brain barrier. At the same time, the aging process in itself promotes reactive oxygen species (ROS), which accumulated and caused mitochondrial dysfunction, lowering VEGF and leading to A $\beta$  deposits, which form plaques and cause Alzheimer's disease [62].

In addition, Zhang et al. recently compared the genetic markers of metabolic syndrome, dementia, and diabetes and found 86 genes common to all 3 diseases, which if combined comprised 43% of the genes known to be associated with dementia, including APOE, APP, PARK2, CEPBP, PARP1, MT-CO2, CXCR4, IGFIR, CCR5, and PIK3CD [63].



Other, less frequent genetic risk factors include phosphatidylinositolbinding clathrin assembly protein (PICALM), CD33, triggering receptor expressed on myeloid cells 2 (TREM2), the ATPbinding cassette transporter ABCA7, clusterin (CLU) and complement receptor type 1 (CR1), all of which are suspected as being involved in the clearance pathways of A $\beta$  [5].

Another important link between metabolic syndromes may lie in microRNA. These tiny RNAs have been accepted as being involved in metabolic syndrome but have also recently been found consistently in Alzheimer's patients. These include hsa-mir-21 (obesity, hypertension, and T2DM), hsa-mir-103<sup>a</sup> (hypertension and diabetes), hsa-mir-17 (hypertension and obesity), hsa-mir-107 (obesity and T2DM), and hsa-mir-20<sup>a</sup> (hypertension). Again, this factor is modifiable with improved metabolic control, and the risk of dementia can be delayed or even eliminated [64].

#### **4. Aging and dementia**

Dementia and especially Alzheimer's disease are more prevalent in aged population. However, not all patients are elderly. In addition, metabolic syndrome as early as adolescence can lead to early or elderly dementia.

One study, conducted on obese New York City minority (Hispanic, African-American) adolescents (average age 16) with and without metabolic syndrome, found that those with metabolic syndrome already showed reduced executive function and cognitive flexibility [65]. The authors suggest that even short-term metabolic alterations at that age would lead to neurological complications. Considering that at that age, white frontal matter is still in a developmental stage, these alterations will have serious effects in later life, leading to early development of dementia and Alzheimer's disease. Another study comparing healthy, obese, and type 2 diabetes adolescents found that both obese and diabetic adolescents (12–18 years) had reduction and alterations in both gray and white matter in the brain. Gray matter volumes in the right hippocampus were reduced in the obese and then diabetic groups [66]. Given these facts, and especially considering the current worldwide epidemics in both obesity and diabetes, interventions need to be initiated very early to avoid the heavy burden of dementia later in life.

It has also been noted that metabolic syndrome in early to middle adulthood causes a high risk of later dementia. Rosanna Tortelli et al. examined the cognitive status of Italian population compared with their metabolic status in a study conducted in 1985. They found that those with insulin resistance or diabetes in 1985 had an increased risk of suffering dementia 20 years later [67]. Chronic metabolic alterations have cardiovascular and believed to be cerebrovascular effects. These include damage to the small vessels in the brain. This leads to white matter damage (including amyloid lesions) and subsequently to dementia. However, it is interesting to note that metabolic syndrome increases the risk of dementia in patients <80 years old, but not older [68, 69]. Another published study, which followed women with metabolic syndrome for 12 years, found that metabolic syndrome increased the risk of dementia almost 2.5 times (OR = 2.47) [70]. Nevertheless, a review of the literature found inconclusive results, possibly due to the variety of definitions, criteria, and testing methods [71]. However, it has been suggested that the events related to metabolic syndrome that are manifested during middle age can develop independent pathways as time progresses, causing the appearance of diagnosable dementia later in life [10].

A study by Phrommintikul et al. [72] compared the factors associated with cognitive decline between younger (<65 years old) and elderly ( $\geq 65$  years) patients with metabolic syndrome. They found that in the younger patients, most of the components of metabolic syndrome, in addition to fibroblast

Gene symbol	Location	Function	References
ApoE	19q13.2	The major cholesterol carrier in the brain	[54, 75]
CLU	8p21-p12	Important role in lipid transport in the brain	[76, 77]
ABCA	9p13.3	Regulate cholesterol homeostasis and transport of high-density lipoprotein cholesterol	[78, 79]
SOTL	9p13.3	Plays a key role in lipid metabolism and A $\beta$ production	[80, 81]
CRI	1q32	Multifunctional mediator of innate immunity involved in amyloid (A $\beta$ ) clearance from brain	[82, 83]
PICALM	11q14	Regulator of brain A $\beta$ production	[84]

**Table 1.**  
*Genes implicated in risk of metabolic syndrome and dementia.*

growth factor 21 (FGF21), were important factors in cognitive decline. However, in the elderly patients, only BMI was a significant factor, indicating that the association between metabolic syndrome and dementia may also be age dependent. Nevertheless, the elderly may also have already suffered damage from the long-term effects of metabolic syndrome. The reasons for this age-dependent difference in the influence of metabolic syndrome remain unknown. On the other hand, a study of elderly Koreans found that metabolic syndrome and vitamin D deficiency were significant risk factors for dementia, increasing the risk threefold. This may be due to the fact that sufficient vitamin D has an anti-inflammatory and therefore protector effect [73]. Other studies exist, but the age cutoff has varied from 65 to 85 years. In all studies, nevertheless, those below the age cutoff showed an association between metabolic syndrome and Alzheimer's, while it had an inverse association in those over the cutoff point used [74]. This fact may also help explain the controversial results reported when trying to associate metabolic syndrome with dementia.

The genes implicated in obesity and metabolic syndrome increased the risk of developing AD in late life (**Table 1**).

### 5. Future and emerging trends

The presence of metabolic syndrome in early and middle adulthood is an important risk factor for developing Alzheimer's disease, as well as various other dementias. Physician's need to be aware of the importance of the presence of these components, not only as risk factors for dementia but also for their significant risk of cardiovascular disease. However, the various components of metabolic syndrome are each modifiable with changes in behavior and lifestyle. Physical activity and weight control are becoming points of emphasis in the attempt to prevent the progression of these diseases, as well as cardiovascular disease and all-cause and cardiovascular mortality.

In addition, some pharmacological treatments have been suggested for metabolic control and subsequent prevention of cardiovascular and dementia complications. These include anti-glucemiant medications, such as metformin, and antihypertensive and anti-inflammatory drugs, such as diuretics and nondihydropyridine calcium channel blocker.

Another emerging strategy involves the genetic risk of dementia. Research is searching for the genetic links between metabolic syndrome and dementia. Those with such genetic backgrounds should be monitored closely.

Finally, the mechanisms of dementia are still not entirely understood. Researchers are trying to unravel the mystery of the brain and its complex relationships, in order to better understand the best strategies to lower the prevalence of cardiovascular disease and to prevent the heartbreaking progression of dementia and especially of Alzheimer's disease.

## 6. Conclusion

In conclusion, it appears clear that the metabolic syndrome and its components increase the risk of developing Alzheimer's disease later in life. Most of these components are modifiable. In addition to the pharmacological treatments, such as the use of diuretics, lifestyle modifications can probably decrease the damage leading to Alzheimer's disease, as well as improving the quality of life of an increasingly older population. An added benefit would be the improvement in cardiovascular condition and the prevention and/or treatment of cardiovascular disease and cardiovascular mortality. Further research is needed to pursue three different avenues: (1) pathophysiology of the metabolic syndrome and dementia; (2) lifestyle interventions for the metabolic syndrome and their effect on the progression of dementia; and (3) the genetic link between the metabolic syndrome, AD, dementia progression, and cardiovascular disease.

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