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Sex Differences in the Preventive Effect of Cardiovascular and Metabolic Therapeutics on Dementia

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Abstract

Dementia is a clinical syndrome characterized by progressive impairment of cognitive and functional abilities. As currently applied treatments for dementia can only delay the progression of dementia and cannot fundamentally cure it, much attention is being paid to reducing its incidence by preventing the associated risk factors. Cardiovascular and metabolic diseases are well-known risk factors for dementia, and many studies have attempted to prevent dementia by treating these risk factors. Growing evidence suggests that sex-based factors may play an important role in the pathogenesis of dementia. Therefore, a deeper understanding of the differences in the effects of drugs based on sex may help improve their effectiveness. In this study, we reviewed sex differences in the impact of therapeutics targeting risk factors for dementia, such as cardiovascular and metabolic diseases, to prevent the incidence and/or progression of dementia.

Key Words: Risk factor for dementia, Sex/gender differences, Therapeutic effect, Cardiovascular disease, Metabolic disease

INTRODUCTION

Dementia is a clinical syndrome characterized by the progressive impairment of cognitive and functional abilities (Silva *et al*., 2019). Annually, there are 9.9 million new cases of dementia, and it is anticipated to affect 115 million more people worldwide by 2050 as a result of aging (Querfurth and LaFerla, 2010), thus making it one of the major health and social challenges of the 21st century. Dementia negatively impacts the quality of life of patients and imposes a significant economic burden on families and society. The global cost associated with dementia in 2015 was 818 billion USD, showing an increase of 35% since 2010. These costs are projected to increase to approximately 2 trillion USD by 2030. Dementia is a major cause of morbidity and mortality in older adults. Unfortunately, the condition is currently incurable, and existing pharmacological and non-pharmacological interventions can only delay its progression (Broadstock *et al*., 2014). Therefore, the lack of fundamental therapeutics for dementia makes treating controllable risk factors a high priority.

Dementia is closely related to various risk factors, including age and several other diseases. Cardiovascular disease (CVD) and metabolic diseases are well-known risk factors for dementia. Several therapeutics for CVD reduce the risk of dementia (Mangmool *et al*., 2017). According to a study by Oxford University, patients with both CVDs and metabolic diseases had a three-fold higher risk of dementia than those solely due to genetic factors (Tai *et al*., 2022). Middle-aged hypertension is a risk factor for both Alzheimer's disease (AD) and vascular dementia, and therapeutics to lower hypertension may be effective in preventing both conditions (Feigin *et al*., 2005). Metabolic diseases such as dyslipidemia, diabetes, obesity, and gout are major risk factors for the development of CVDs and are known to impair cognitive function through multiple mechanisms (Yokomichi *et al*., 2017). Upon analyzing the correlation between metabolic syndrome and the risk of dementia, the group diagnosed with metabolic syndrome for four years presented a 1.35-fold higher risk of dementia from all causes than the group that had never been diagnosed with metabolic syndrome. In this context, preventing CVD and metabolic diseases is likely to reduce the burden of dementia.

The importance of sex differences in human pathophysiol-

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ogy has been demonstrated; however, most animal studies and clinical trials have been conducted in males, considering that males are representative of humans. Indeed, 22% of therapeutic-related reports lacked sex-specific effectiveness data, and 17% omitted sex-related safety data for new drug applications (Harris and Douglas, 2000). Accumulating evidence suggests that sex/sex-related issues are an important consideration in clinical practice as they can influence medical care, individual medication choices, and patient outcomes. Several studies have reported sex-specific differences in the efficacy and toxicity of various therapeutic agents. Furthermore, a previous study by our group showed that the reduction in AD risk induced by statin use in patients with ischemic heart disease (IHD) was sex-specific (Zissimopoulos *et al*., 2017). Therefore, a better understanding of sex-specific differences in efficacy may help improve the efficacy of drugs in males and females separately and provide a potential therapeutic strategy.

This study aimed to review sex differences in the impact of therapeutics targeting risk factors for dementia, including cardiovascular and metabolic diseases, on dementia incidence.

SEX DIFFERENCES IN THE EFFECTS OF THERAPEUTICS ON DEMENTIA

Dementia is a major public health concern in an aging society, with AD accounting for 60%-80% of cases. AD is characterized by the buildup of amyloid-β (Aβ) plaques and hyperphosphorylation of tau protein, observed as neurofibrillary tangles (NFTs) (Oveisgharan *et al*., 2018). According to several studies on the biological and clinical effects of sex differences on dementia, dementia occurs more frequently in women than men (Canevelli *et al*., 2017). Women are more often diagnosed with a more severe form of AD pathology, characterized by markedly noticeable NFTs and neuritic plaques, than men (Barnes *et al*., 2005). The prevalence of tau pathology is higher in women than men (Oveisgharan *et al*., 2018). Numerous studies have confirmed that AD pathology, including brain structure and function, varies by sex, as do the differences in risk factors. However, considering sex differences in modulating patient responses to therapeutics in AD clinical trials is undervalued. Currently, cholinesterase inhibitors (ChEIs) such as donepezil, rivastigmine, galantamine, and the N-methyl-d-aspartate (NMDA) receptor antagonist memantine have been approved by the US Food and Drug Administration (FDA) for the treatment of AD, and aducanumab and lecanemab have also been approved as monoclonal antibody therapies for AD (Verger *et al*., 2023).

The cause of dementia may also differ based on sex, which could contribute to the difference in the prevalence of dementia between the sexes, thereby leading to differential therapeutic effects. In this chapter, we summarize sex differences in the effects of dementia therapeutics on dementia (Table 1).

Cholinesterase inhibitors (ChEIs)

ChEIs reduce the breakdown of acetylcholine in the brain, preserving cognitive functions and improving the cognitive, behavioral, and neuropsychiatric symptoms of AD (Coker-Ayo *et al*., 2022). Patients diagnosed with mild-to-moderate AD are prescribed galantamine, rivastigmine, and/or donepezil as first-line therapeutics (Calabria *et al*., 2009). Several studies have reported sex-specific therapeutic effects of ChEIs.

Galantamine: Galantamine was approved in 2000 for the treatment of individuals with mild-to-moderate AD (Marucci *et al*., 2021). It acts by increasing the synaptic levels of acetylcholine, reducing central cholinergic neurotransmission by reversibly inhibiting acetylcholinesterase (AChE) rather than butyrylcholinesterase (BuChE), and altering nicotinic cholinergic receptors (Li *et al*., 2019). Considering that the loss of neurons expressing nicotinic receptors leads to severe cognitive dysfunction, the ability of galantamine to modify these receptors may contribute to its clinical effectiveness (Marucci *et al*., 2021). The administration of three doses of galantamine (8, 16, and 24 mg/day) was investigated in a Korean population with mild-to-moderate AD. All three doses improved cognitive functioning in a dose-dependent manner, with the best efficacy observed at 24 mg/d compared to that in the control group. While these effects did not differ between the sexes (Suh *et al*., 2004), a short-term beneficial response to galantamine was observed in men but not in women. It was presumed that physiological factors, such as sex hormones, and structural differences, such as the large cerebral hemisphere of men, could play a role in the sex differential effects of drugs (Wattmo *et al*., 2011). Galantamine is also used to treat mild cognitive impairment (MCI) in Hispanic men, while it is used to treat MCI-AD in African-American women. These differences in sex demographics and ethnicity highlight the importance of tailoring treatment for patients diagnosed with AD (Coker-Ayo *et al*., 2022).

Rivastigmine: Rivastigmine is used as a treatment for mild-to-moderate AD and acts as a “pseudo-irreversible” selective inhibitor of AChE and BuChE (Coker-Ayo *et al*., 2022). Oral administration of rivastigmine for 26 weeks (Calabria *et al*., 2009) and oral administration of high-dose rivastigmine improve cognitive function (Szeto and Lewis, 2016). In addition, using rivastigmine as a transdermal patch instead of taking it orally significantly improves the behavioral and psychological symptoms of mild-to-moderate AD (Colombo *et al*., 2018). Several studies conducted on advanced AD have suggested that ChEIs elicit more positive responses in men than in women (Canevelli *et al*., 2017). In contrast, one study suggested that survival after treatment was longer in women than in men (Wattmo *et al*., 2014), and another study stratified by sex showed a more protective effect in women than in men (Scacchi *et al*., 2014); these findings suggest sex differences in the effects of anti-dementia drugs. Upon administering rivastigmine to individuals with MCI for 3-4 years, the progression of AD was significantly reduced in women but not in men (Ferris *et al*., 2009). However, this result may be because of the faster progression of dementia in women than in men, suggesting that rivastigmine may affect men with rapidly progressing dementia (Ferris *et al*., 2009). However, further studies are needed to confirm this hypothesis. Since studies based on sex-specific differences have not been conducted for the use of rivastigmine in the later stages of dementia, the beneficial effect observed might be the result of the different rates of AD progression in both sexes rather than the effect of therapeutics.

Donepezil: Donepezil is the most frequently prescribed drug approved for all stages of AD. It is a potent, centrally acting, selective, rapid, and reversible AChE inhibitor (Szeto and Lewis, 2016). It decreases amyloid precursor protein levels and neuronal injury, modifies cholinergic action, and upregulates nicotinic expression in the cortex (Jacobson and

Table 1. Sex differences in the effect of dementia therapeutics

Classification	Dementia therapeutics	Therapeutic effect on dementia		Age (years)	Note	Reference
		Men	Women			
Cholinesterase Inhibitors	Galantamine	++	+	73.9 ± 7.1	Men displayed a more beneficial effect than women in the short-term response of galantamine	Wattmo *et al*., 2011
	Rivastigmine	+	++	75.4 ± 7.5	Women displayed a better response to treatment with rivastigmine than men	Scacchi *et al*., 2014
		+	++	70.3 ± 7.9	Women patients with mild cognitive impairment prescribed with rivastigmine for 3-4 years showed decreased progression of AD	Ferris *et al*., 2009
	Donepezil	+	+	75.1 ± 5.0	No differences in the cognitive and functional effects of donepezil were found between men and women	Canevelli *et al*., 2017
		+	++	79.7 ± 6.9	Women are more sensitive than men to treatment with donepezil	Scacchi *et al*., 2014
		++	+	75.1 ± 5.0	In animal studies, males were more sensitive to donepezil treatment than females	Giacobini and Pepeu, 2018
		+	++	78.7 ± 7.5	Co-treatment with donepezil and rivastigmine showed a better response in women than in men	Scacchi *et al*., 2014
NMDA antagonist	Memantine	+	+	76.2 ± 4.3	Memantine displayed a preventive effect against dementia, but there was no difference between men and women	Canevelli *et al*., 2017
Anti-Aβ monoclonal antibody	Aducanumab	+	+	70.6 ± 7.5	A 22% decline in CDR-SB was prevented by aducanumab, but no differences were found between men and women	Budd Haeberlein *et al*., 2022
	Lecanemab	+	+	72.5 ± 12.5	A 27% decline in CDR-SB was prevented by lecanemab, but no differences were found between men and women	Shi *et al*., 2022

+, significantly effective; ++, effective to a greater extent; AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating-Sum of Boxes.

Sabbagh, 2008). Although some studies have suggested that donepezil treatment may be more effective in males owing to morphological, functional, and hormonal brain differences (Giacobini and Pepeu, 2018), other studies have reported a better response to the drug in women because of the ESR1 genotype with the P allele (Scacchi *et al*., 2014) or no significant differences among the effects between the sexes (Canevelli *et al*., 2017). Thus, sex differences in donepezil treatment show contradictory results. Owing to the lack of data on sex differences in the effects of this drug in clinical trials, appropriate studies are needed. Additionally, sex differences have been observed after the administration of donepezil in combination with other ChEIs. For example, individuals diagnosed with moderate-to-severe cognitive impairment benefit from a combination of donepezil and memantine, whereas those with mild-to-moderate cognitive impairment benefit from a combination of donepezil and transdermal rivastigmine (Colombo *et al*., 2018). Although logistic regression analysis showed that the response to ChEIs was 73% higher in men than in women (MacGowan *et al*., 1998), co-administration of donepezil and rivastigmine was more effective in preventing dementia in women than in men (Scacchi *et al*., 2014). Despite these conflicting results, sex differences in the therapeutic effects indicate the need for sex-specific dosing.

N-methyl-d-aspartate (NMDA) receptor antagonist

NMDA receptors are involved in neurotransmission, learning, memory processes, and regulation of neuroplasticity in the brain (McShane *et al*., 2019). Overstimulation with glutamate, the main excitatory neurotransmitter in the central nervous system, leads to nerve cell damage (Lipton and Rosenberg, 1994). NMDA receptor antagonists delay the progression of dementia by reducing neuronal loss and inhibiting excessive glutamate activity (Ellison, 1995). Memantine is a symptomatic treatment for AD that targets the N-methyl-d-aspartate (NMDA) receptors.

Memantine: In 2003, memantine was approved as a therapeutic agent for moderate-to-severe AD. Memantine is classified as an uncompetitive NMDA antagonist for the treatment of AD (Danysz *et al*., 2000). It is prescribed as a monotherapy agent or in combination with AChE inhibitors that slow down the rate of dementia by preventing the activation of NMDA receptors (Coker-Ayo *et al*., 2022). The mechanism of action of memantine involves the prevention of overstimulation of glutamatergic neurons, which results in excitotoxicity (McShane *et al*., 2019). Stimulation of synaptic NMDA leads to neuroprotection. In contrast, the stimulation of extrasynaptic NMDA receptors results in cell death and increases amyloid production (McShane *et al*., 2019). Thus, by preventing the stimulation of extrasynaptic NMDA receptors, memantine exerts its effects by reducing tau phosphorylation or amyloid toxicity (Song *et al*., 2008). Overall, memantine can be recommended as an initial treatment for AD, a claim supported by various studies.

C_{max} and area under the memantine curve are higher for women than men; however, these differences do not persist after adjusting for body weight. Memantine also shows higher oral clearance (CL/F) in men. However, despite sex differences in the pharmacokinetic properties of memantine, the effect is observed at a similar dose in both men and women, with no differences between women (Canevelli *et al*., 2017). In another study, the administration of memantine in combination with vitamin D supplementation to individuals with AD showed no sex differences (Annweiler *et al*., 2012).

Anti-amyloid-β monoclonal antibodies (mAbs)

The main pathological features of AD comprise Aβ plaque deposits and NFTs formed by the hyperphosphorylated tau protein (van Dyck, 2018). The majority of putative disease-modifying therapies for the incidence of AD are directed against the Aβ peptide. Among the various anti-Aβ therapeutic approaches, the most extensively developed is immunotherapy-specific passive immunization by administering exogenous mAbs (van Dyck, 2018). Passive immunization with mAbs can clear Aβ plaque deposits and NFTs, either directly or through microglia/complement activation, thereby halting the amyloid cascade and preventing neurodegeneration and cognitive/functional decline (Shi *et al*., 2022). Recently, disease-modifying therapies that can change the underlying pathophysiology of AD by using anti-Aβ mAbs (*e.g.*, aducanumab and lecanemab) have been developed successfully.

Aducanumab: Aducanumab is a new recombinant human mAb therapy approved by the US and FDA in 2021 for the treatment of AD (Yang and Sun, 2021). Aducanumab can be prescribed to individuals newly diagnosed with MCI and can be combined with ChEI or memantine for individuals with early-stage AD (Cummings *et al*., 2021). Aducanumab acts by penetrating the blood-brain barrier and selectively binding to soluble oligomers and insoluble fibrils that form amyloid plaque deposits in neuronal tissues (Behl *et al*., 2022). The results of the phase 3 clinical trial, EMERGE, showed that aducanumab increased the clinical dementia rating-sum box (CDR-SB) score by 0.39 points in the high-dose aducanumab group (10 mg/kg), compared to that in the control group, for more than 76 weeks. This implies 22% less degradation (Budd Haeberlein *et al*., 2022). However, aducanumab is associated with adverse events known as amyloid-related imaging abnormalities (Scacchi *et al*., 2014), which can be observed using magnetic resonance imaging. ARIA-E and ARIA-H appear when the blood-brain barrier is damaged in the process of immune-mediated clearance, which removes amyloid accumulated in the brain with targeted therapy. ARIA-E is characterized by vasogenic brain edema, while ARIA-H is characterized by the deposition of hemosiderin, which presents as microhemorrhages in the brain (Cummings *et al*., 2021). Studies on sex differences in the anti-dementia effects of aducanumab have not been conducted. Aducanumab requires further clinical studies and an appropriate outline of its use, which ultimately requires more time, resources, and plans of action. Moreover, there is a need to conduct sex- and gender-based studies to ensure the proper and safe use of aducanumab in the healthcare system.

Lecanemab: Lecanemab is the second anti-Aβ drug approved by the FDA after aducanumab in January 2023 (Verger *et al*., 2023). Lecanemab can reduce pathogenic Aβ, prevent Aβ deposition, and selectively reduce Aβ fibrils in the brain and cerebrospinal fluid of AD animal models (Verger *et al*., 2023). A phase 3 Clarity AD clinical trial of lecanemab, an amyloid-targeting antibody, showed some clinical benefits in individuals with AD (Thambisetty and Howard, 2023). Lecanemab began changing the global CDR-SB after 6 months of treatment and reduced disease progression by 27% compared to placebo after 18 months. The incidence of ARIA-E is 12.5% with lecanemab, 1.7% with placebo, and 35% with aducanumab (Prins and Scheltens, 2013). Lecanemab ap-

pears to be the most promising treatment for AD among mAbs due to its effects of reduction in brain Aβ levels, alleviation of cognitive decline, and low incidence of ARIA-E. It also has moderate therapeutic effects and improved safety (Shi *et al*., 2022). However, the results of several clinical trials have been largely negative and have not shown clinically evident or relevant effects in individuals with prodromal dementia. However, the efficacy and safety of lecanemab require further investigation (Shi *et al*., 2022). Similar to aducanumab, studies on sex differences in the antidementia effects of lecanemab have not been conducted. The availability of lecanemab offers new opportunities for AD management. However, further clinical studies, guidelines, and sex-based studies are needed to safely integrate its use into the healthcare system.

SEX DIFFERENCES IN THE EFFECTS OF CARDIOVASCULAR THERAPEUTICS ON PREVENTION AGAINST DEMENTIA

CVDs are the leading cause of death worldwide. Approximately 17.9 million people died from CVDs in 2019, accounting for 32% of deaths worldwide (Kim, 2021). CVDs, including hypertension, IHD, and atrial fibrillation (AF), are well-known risk factors for dementia. The US Cardiovascular Health Study Cohort confirmed that the lower the cognitive score, the higher the incidence of dementia in individuals with chronic coronary artery disease; however, no difference was observed between men and women (Newman *et al*., 2005). In contrast, according to an aging study by Aronson *et al*. (1990), older women with a history of myocardial infarction had a 5-fold increased risk of dementia compared to men (Aronson *et al*., 1990). This suggests that women with cardiomyopathy are particularly vulnerable to dementia. Therefore, to reduce the risk of dementia and prevent dementia in individuals with CVDs, it is important to study the sex-specific differences in the efficacy of cardiovascular drugs in preventing dementia. This chapter describes sex differences in therapeutics targeting CVDs, which are risk factors for dementia (Table 2).

CVDs as risk factors for dementia

High blood pressure is a well-known risk factor for cerebrovascular disorders, including cerebral infarction, stroke, and dementia. Middle-aged women with high blood pressure have a 73% higher risk of dementia than middle-aged women with normal blood pressure; however, a similar increase in hypertension has not been found to increase the risk of dementia in men (Gilsanz *et al*., 2017). Hypertension increases vascular dementia in both men and women, but the association between hypertension and the risk of AD weakens in those aged >65 years and reaches significance only in men aged <65 years (Kimm *et al*., 2011).

IHD, also known as coronary artery disease, is a condition in which the heart arteries are narrowed, resulting in insufficient blood supply to the heart and its muscles. The narrowing of blood vessels is mainly caused by the formation of plaques, a condition known as atherosclerosis, with blood clots and constriction of blood vessels (Institute of Medicine Committee on Social Security Cardiovascular Disability, 2010). When blood vessels in the heart are completely blocked, the heart muscles die, resulting in myocardial infarction. Because of this risk, IHD contributes to mortality worldwide and causes dementia by reducing cerebral blood flow using narrowed blood vessels, which disrupts the homeostasis of cerebrovascular vessels, thereby increasing the accumulation of Aβ and tau and reducing cognitive functioning (Justin *et al*., 2013).

AF is the most persistent type of arrhythmia in the older adult population. This condition can cause blood clots in the heart and increase the risk of complications such as stroke and heart failure (Kim *et al*., 2019). During AF, the atria and ventricles do not match and beat chaotically and irregularly. AF is generally not life-threatening but requires appropriate treatment to prevent complications such as stroke. Since AF can cause complications, such as stroke and cerebral hypoperfusion, it has been suggested as a risk factor for dementia (Bunch *et al*., 2020). The increased risk of brain injury is attributed to several potential pathways, including giant thrombosis, hemorrhage, cerebral hypotension, and systemic hypotension. A 20-year prospective population-based study in Rotterdam found that the prevalence of AF was associated with an increased risk of dementia, particularly in younger participants and those with a longer duration of AF inflammation (de Bruijn *et al*., 2015). Few studies have examined the relationship between sex, AF, and the risk of dementia or cognitive impairment.

Calcium channel blockers (CCBs): CCBs are used as first-line anti-hypertensive medications to reduce high blood pressure. CCBs disrupt calcium transport through calcium channels, thereby reducing blood pressure through the vascular smooth muscle and leading to an increased arterial diameter (Nimmrich and Eckert, 2013). Intracellular calcium is necessary for various signal transduction pathways, where it serves as a secondary messenger. Balanced intracellular calcium levels must be maintained to constantly regulate neuronal function (Kalar *et al*., 2021). However, with aging, the regulation of intracellular calcium is impaired, causing neuronal dysfunction and making it a risk factor for AD incidence through the build-up of Aβ inducing an influx of extracellular calcium. *In vitro* studies have shown that CCBs provide neuroprotection and reduce Aβ build-up by inhibiting platelet activation. With vascular dementia accounting for 25% of dementia cases caused by cerebral hypoperfusion, CCB use may prevent AD through cerebral vasculature relaxation and improved perfusion (Wu and Wen, 2016). The demand to reduce the risk of dementia in older adults with hypertension is now being prioritized. A follow-up study observed a significantly reduced incidence of dementia in individuals using CCBs compared with non-users. Interestingly, a longer exposure to CCB treatment decreases the risk of developing dementia. In addition, patients who adhered to a regimen of increasing CCB doses during the entire treatment period had a slightly lower risk of developing dementia (Wu and Wen, 2016). Based on these observations, it can be concluded that using CCBs has a lowering effect on blood pressure and a beneficial effect on preventing dementia. Another study found that the use of increasing doses of amlodipine, the most frequently administered CCB in patients with hypertension, was associated with a decreased risk of AD but not vascular dementia, compared to the use of other CCBs (Kalar *et al*., 2021). In an age-based study of individuals treated with CCB, the risk of dementia was reduced in individuals with hypertension aged >60 years (Feldman *et al*., 2016). Owing to its safe and tolerable characteristics, amlodipine can be considered a good alternative for managing hypertensive individuals with dementia. Nevertheless, additional studies

Table 2. Sex differences in the effects of cardiovascular therapeutics on prevention against dementia

Cardiovascular disease	Therapeutics	Therapeutic effect on dementia		Age (years)	Note	Reference
		Men	Women			
Hypertension	Calcium channel blocker	+	+	70 ± 10	Amlodipine had a lower incidence of dementia compared to non-users, but there was no difference between men and women	Kalar *et al.*, 2021
	Diuretic	+	+	74.9 ± 6.4	Thiazides and potassium-sparing diuretics reduced the incidence of dementia, but there was no difference between men and women	Chuang *et al.*, 2014
	Angiotensin converting enzyme inhibitor (ACEI)	+	+	65 ≤aged	Captopril and perindopril improved early cognitive function in AD patients, but there was no difference between men and women	Fazal *et al.*, 2017
		+	N.S.	50 ≤aged	ACEIs displayed significant protective effect in men, but not in women	Ho *et al.*, 2021
		+	+	65.2 ± 9.5	ACEIs displayed a preventive effect against dementia, but there was no difference between men and women	Kuan *et al.*, 2016
	Angiotensin receptor blocker (ARB)	+	+	74 ± 5.5	Candesartan and irbesartan showed a preventive effect against dementia, but there was no difference between men and women	Li *et al.*, 2010
		+	+	67 ≤aged	ARBs showed a protective effect against dementia in white men, white women, and black women	Barthold *et al.*, 2018
		+	+	64.9 ± 9.4	ARBs showed a preventive effect against dementia, but there was no difference between men and women	Kuan *et al.*, 2016
Ischemic heart disease	Cyclooxygenase inhibitor	N.S.	+	72.7 ± 5.6	Low-dose aspirin reduced the risk of dementia in women, but not in men	Matsumoto *et al.*, 2020
		+	+	66.9 ± 7.9	A daily dose of 40 mg aspirin decreased the risk of developing AD	Chang *et al.*, 2016
	Phosphodiesterase 3 inhibitor	N.S.	+	75 ± 10	Cilostazol showed preventive effects against dementia only in women, but not men	Kim *et al.*, 2018
Atrial fibrillation	Non-vitamin K oral antico-agulant	+	+	63 ± 10	Rivaroxaban, edoxaban, apixaban, dabigatran showed a preventive effect against dementia, but there was no difference between men and women	Dentali *et al.*, 2015

+, significantly effective on prevention against dementia; AD, Alzheimer's Disease; N.S., not significant.

are required to confirm the possible mechanisms underlying the beneficial effects of CCBs in preventing dementia. In terms of sex differences in hypertension treatment, the bioavailability (AUC and C_{max}) of amlodipine was higher in women than in men, as was the change in blood pressure (Kalibala *et al*., 2020). However, no difference in the preventive effects of amlodipine against dementia incidence was noted (Kalar *et al*., 2021).

Diuretics: Diuretics effectively lower blood pressure in individuals with hypertension and reduce the risk of adverse cardiovascular events in adults with hypertension (Blowey, 2016). Diuretics reduce blood pressure by increasing sodium emissions and reducing sodium reabsorption in the renal tubes (Roush *et al*., 2014). Diuretic prescriptions are higher in women than men (Gu *et al*., 2008); this sex difference is because it has more beneficial effects in women. In fact, diuretics have beneficial effects on reducing the renal excretion of calcium as well as the risk of decreased bone density and fracture in postmenopausal women (Thoenes *et al*., 2010). However, blood pressure control with diuretics is better in men than in women (men: 54.6%, women: 44.2%) (Gu *et al*., 2008). In addition to their anti-hypertensive effect, diuretics exert a preventive effect on dementia (Chuang *et al*., 2014). Among the three subclasses of diuretics (thiazide, potassium-sparing, and loop diuretics), this preventive effect is driven by thiazide- and potassium-sparing diuretics, which show a 30% reduction in the risk of AD (Chuang *et al*., 2014). The protective effect of diuretics on dementia is supported by the fact that the potassium level plays a significant role in cognitive decline and that a decreased level of cerebrospinal fluid $A\beta_{1-42}$ (a biomarker for AD) is associated with hypokalemia (Mielke *et al*., 2006). However, no sex-related differences were observed between the use of diuretics and the prevention of AD.

Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB)

The renin-angiotensin system (RAS) plays an important role in regulating blood pressure homeostasis; therefore, RAS inhibitors are commonly prescribed for chronic hypertension. Two types of RAS inhibitors, ACEIs and ARBs, lower blood pressure by inhibiting the RAS (Barthold *et al*., 2018). ACEIs and ARBs have beneficial effects in the prevention of dementia and hypertension. In a comparative study, ARBs showed more significant preventive effects against all-cause dementia than ACEIs (40% decrease by ARBs *vs.* 26% decrease by ACEIs), whereas both RAS inhibitors showed a similar effect on vascular dementia (59% reduction by ARBs *vs.* 58% reduction by ACEIs) (Kuan *et al*., 2016). Because ARBs exhibit a protective effect similar to that observed upon treatment with a higher dose of ACEIs for a longer duration, ARBs are preferred for preventing dementia (Kuan *et al*., 2016). However, since ACE contributes to the degradation of Aβ, it has been suggested that ACEIs could adversely alter the ACE-mediated degradation of Aβ in the brain (Barthold *et al*., 2018). However, data on the efficacy of RAS inhibitors is limited. In a bioequivalence study, enalapril, an ACEI, was administered to healthy subjects, and no sex differences were observed in its pharmacokinetics (Zapater *et al*., 2004). However, there were sex differences in its pharmacodynamics; considering the plasma concentration of enalaprilat (an active metabolite), the minimal ACE activity was lower in women below that concentration; however, at higher concentrations, both men and women displayed the same level of ACE inhibition. At maximal inhibition of ACE activity, systolic blood pressure and ACE activity were lower in women at all enalaprilat concentrations (Zapater *et al*., 2004). Studies evaluating sex differences in the pharmacokinetics of commonly used ARBs have found higher overall C_{max} and AUC in women. Although these values did not show significance after adjusting for weight, the C_{max} of telmisartan, an ARB, was higher in women than men. This is attributed to its slower clearance, similar to that of other drugs metabolized by conjugation or oxidation (Kalibala *et al*., 2020) . The use of ARBs showed a significant protective effect against AD in Caucasian men, Caucasian women, and Black women; however, no association was observed in Hispanic men and women, and little is known about ethnic differences (Barthold *et al*., 2018). Regarding sex differences in the prevention of dementia, no difference between men and women users of candesartan and irbesartan (Li *et al*., 2010) was reported. ACEIs, such as captopril and perindopril, improve early cognitive function in patients with AD; however, there are no differences between men and women (Fazal *et al*., 2017). However, other studies have shown that ACEIs have a slight neuroprotective effect in men but not women (Ho *et al*., 2021).

Cyclooxygenase inhibitor (aspirin): Aspirin is commonly prescribed for the secondary prevention of CVDs. It possesses anti-inflammatory and antithrombotic properties that allow it to play a vital role in the treatment of various diseases (Li *et al*., 2020). Owing to its antithrombotic effects, low-dose aspirin offers protection against AD by improving platelet and endothelial function (Broe *et al*., 2000). Furthermore, reports show that aspirin displays a neuroprotective effect against dementia by reducing NFTs, degrading cerebral Aβ peptide levels, and modulating synaptic plasticity. It regulates cerebral blood flow and prevents stroke in patients with cerebrovascular diseases (Li *et al*., 2020). Aspirin is known to activate platelets more in men than women, but low-dose aspirin therapy reduces platelet activity to similar levels (Rosano *et al*., 2015). Aspirin had no effect on myocardial infarction (a type of IHD) in women but showed a 32% reduction in men (Berger *et al*., 2006). In contrast, aspirin showed a preventive effect in women but not men in stroke (Rosano *et al*., 2015). A retrospective study found that low-dose aspirin (40 mg/day) is associated with a reduced incidence of AD in patients with type-2 diabetes (T2D) (Chang *et al*., 2016). Women who used low-dose aspirin tended to have a lower incidence of dementia than non-users, with no differences observed in men (Matsumoto *et al*., 2020). However, a higher dose of 80 mg/day can potentially increase the risk of AD in patients with T2D, while 40 mg/day showed a protective effect in preventing AD (Chang *et al*., 2016). In addition to its effects on CVDs, the anti-inflammatory effect of aspirin might contribute to the difference in its action between the sexes. Further investigations are required to clarify the mechanisms underlying this effect.

Cilostazol: Cilostazol is a phosphodiesterase (PDE) inhibitor that inhibits platelet aggregation and induces peripheral vasodilation by increasing the concentrations of intracellular cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (Ono and Tsuji, 2019). It is prescribed for the treatment of IHD. Increased cAMP levels mediated by PDE inhibitors activate protein kinase A, leading to the phosphorylation of cAMP response element-binding protein (CREB). CREB phosphorylation activates various target genes that trigger the synthesis of new proteins, strengthen

existing synaptic connections, and create synapses related to memory consolidation. Through these mechanisms, PDE inhibitors improve long-term memory and exert neuroprotective effects (Kinney *et al*., 2018). Cilostazol reduces the accumulation of Aβ and displays a protective effect against Aβ-induced cognitive impairment in experimental models (Kim *et al*., 2018) . In fact, cilostazol has a stable clinical effect on cerebral circulation and Aβ metabolism in patients with AD, thereby reducing the possibility of cognitive function deterioration (Tai *et al*., 2017). Because the sex-specific effects of cilostazol on hypertension were not addressed in this study, it is important to further investigate these effects. In a recent study, cilostazol showed a preventive effect against dementia, and an analysis based on sex showed a significant effect in women but not in men. In particular, women treated with cilostazol for more than two years showed a significantly lower risk of developing dementia (Kim *et al*., 2018). It is conceivable that sex-related differences in the protective effects of cilostazol may be due to sex-related pathophysiological and hormonally modulated pharmacological/metabolic differences. However, the relationship between hormonal therapy and memory loss and dementia remains unclear.

Non-Vitamin K Oral anticoagulant (NOAC): For a long time, warfarin had been the therapeutic basis for preventing stroke until NOACs entered the healthcare system (Hsu *et al*., 2021). Unlike warfarin, NOACs are safe and effective, with a lower risk of microvascular bleeding and other side effects (Hsu *et al*., 2021). NOACs act through two inhibitory mechanisms: thrombin and direct factor Xa inhibitors. Thrombin inhibitors directly bind to thrombin, inhibiting coagulation and preventing thrombin from breaking fibrinogen into fibrin (Paul *et al*., 2020). Direct factor Xa inhibitors inhibit factor Xa, which is a trypsin-like serine protease. They play an important role in linking the final common coagulation pathways among the intrinsic and extrinsic pathways and directly bind to factor Xa, thereby preventing the cleavage of prothrombin into thrombin (Paul *et al*., 2020). Numerous studies have shown that NOAC use in patients with AF is associated with a reduced incidence of dementia. NOACs lower the risk of dementia by 22% compared to warfarin, with warfarin showing a higher risk of microbleeds that cause brain damage, possibly leading to dementia (Kim *et al*., 2021). It is not yet clear how NOACs prevent dementia, but the reason may be linked to their anti-inflammatory and antioxidant activities, which improve endothelial dysfunction and prevent microembolisms (Kim *et al*., 2021). Upon investigating patients with AF who were prescribed NOACs, the efficacy of NOACs was similar in both men and women, with no difference in safety between the sexes. However, when NOACs were administered for prolonged treatment of venous thromboembolism, there was a tendency towards an increased risk of bleeding in men than in women (Dentali *et al*., 2015). Further studies are needed to determine the effect of sex-specific differences on the use of NOACs in the therapeutic treatment of dementia.

SEX DIFFERENCES IN THE EFFECTS OF METABOLIC THERAPEUTICS ON PREVENTION AGAINST DEMENTIA

Metabolic diseases, including dyslipidemia, diabetes, obesity, and gout, are major public health issues worldwide. Various studies have reported an association between metabolic diseases and dementia. Furthermore, sex-related differences have been observed in the incidence of dementia in individuals with metabolic diseases. Therefore, developing effective methods to reduce the risk of dementia in patients with metabolic diseases while considering sex differences is of clinical importance. In this context, we assessed whether the use of therapeutic agents in patients with metabolic diseases was associated with a lower risk of developing dementia and whether there were differences between men and women in terms of the effect (Table 3).

Metabolic diseases as risk factors for dementia

Dyslipidemia, a disorder of lipoprotein metabolism that includes lipoprotein overproduction or deficiency, is an important risk factor for dementia (Ancelin *et al*., 2013). The prevalence of dyslipidemia is higher in men than in women (Kastarinen *et al*., 2000), which may be because men are predisposed to developing coronary heart diseases (Stern *et al*., 2000), with dyslipidemia being a contributing factor. Various studies have suggested a close relationship between lipid levels and vascular changes that occur in dementia (Olmastroni *et al*., 2022). However, the prevalence of dementia in patients with hyperlipidemia differs according to sex. Women with high triglyceride and low-density lipoprotein cholesterol levels showed a significant cognitive decline, whereas no difference was reported in men (Liu *et al*., 2020). Cholesterol levels are particularly elevated and prevalent in midlife, potentially contributing to an increased risk of dementia through damage to the brain vasculature. Therefore, reducing cholesterol levels is thought to reduce the risk of dementia (Olmastroni *et al*., 2022).

Diabetes is a chronic metabolic disease caused by elevated blood glucose levels resulting from dysfunctional insulin secretion (Natesan and Kim, 2023). According to the Non-Communicable Diseases Risk Factor Collaboration, diabetes is predominantly observed to increase in men (9%) compared to women (8%) in middle-aged populations (Tramunt *et al*., 2020). Sex hormones, specifically estrogen, have a protective role in women, and the decrease in their levels during the menopausal stage plays a critical role in susceptibility to T2D (Tramunt *et al*., 2020). In contrast, men with low testosterone levels have an increased risk of developing T2D and vascular diseases (Tramunt *et al*., 2020). Several studies have demonstrated the link between diabetes and dementia. Diabetes increases oxidative stress and glycation levels. Ultimately, there is an increase in advanced glycation end products in cell tissues, causing microvascular complications, as well as increased amyloid accumulation, NFTs, and oxidative damage, thereby increasing the risk of dementia (Singh *et al*., 2001). Insulin plays an important role in the digestive system and the brain. In AD, many of the functions of the brain are impaired, including learning and memory, neuroinflammation, and Aβ clearance and phosphorylation of tau, which are regulated by insulin as well (Duarte *et al*., 2012), thereby indicating that it is a factor connecting T2D and AD. Patients with diabetes have a two-fold higher risk of developing vascular dementia and a 1.6-fold higher risk of developing AD than non-diabetic patients. Furthermore, a greater diabetes-related risk of vascular dementia has been reported in women than in men (Chatterjee *et al*., 2016).

The worldwide obesity rate has tripled since 1975 and is reported to be a major cause of metabolic diseases (Hwang *et*

Table 3. Sex differences in the effects of metabolic therapeutics on prevention against dementia

Metabolic disease	Therapeutics	Therapeutic effect on dementia		Age (year)	Note	Reference
		Men	Women			
Dyslipidemia	HMG-CoA reductase inhibitor	+	+	72.1 ± 5.4	For men, atorvastatin, rosuvastatin, and pravastatin showed significant effects, and for women, rosuvastatin, pravastatin, and lovastatin showed significant effects	Kim *et al*., 2020
Diabetes	α-glucosidase inhibitor	+	++	59.8 ± 0.1	Acarbose displayed a beneficial effect against dementia in women, but a neutral effect in men	Tseng, 2020
	PPAR-γ agonist	+	+	50 ± 10	Pioglitazone was effective in preventing the incidence of dementia in a time- and dose-dependent manner, but there was no difference between men and women	Chou *et al*., 2017
	Incretin mimetic	N.S.	+	70.7 ± 4.3	A reduction in dementia was found in exenatide users, specifically women	Zhou *et al*., 2021
	Biguanide	N.S.	+	80 ± 10	In women, overall cognitive and executive function decreased more significantly in the non-users compared to the metformin-users	Samaras *et al*., 2020
Obesity	Incretin mimetic	+	+	56.5 ± 7.5	Duration of liraglutide treatment in men was associated with improved cognitive performance	Vadini *et al*., 2020
Gout	Xanthine oxidase inhibitor	+	+	76.0 ± 7.4	High doses of allopurinol (>200 mg/d) and febuxostat (40 mg/d) reduced the incidence of dementia, but there was no difference between men and women	Singh and Cleveland, 2018c
	Uricosuric drug	++	+	76.9 ± 7.1	Benzbromarone reduced the incidence of dementia more in men than in women, but only for 180 days	Chuang *et al*., 2020

+, significantly effective on prevention against dementia; ++, effective on prevention against dementia to a greater extent; N.S., not significant.

al., 2021). Obesity is a complex disease commonly observed in women due to the fat storage necessary for reproduction and lactation (Lovejoy *et al*., 2009). The differences between men and women are partly mediated by sex hormones and aging (Kapoor *et al*., 2017). In addition, women are more prone to weight gain owing to changes in estrogen levels during the perimenopausal and postmenopausal periods (Porter *et al*., 2020). Obesity, independent of other cardiovascular risk factors, is associated with cognitive decline and is a risk factor for dementia (Elias *et al*., 2003). In particular, it has been reported that older women with a higher body mass index and obesity rate have a higher risk of AD compared to men (Li *et al*., 2017).

Gout occurs in individuals with hyperuricemia or increased serum urate concentrations, accumulating monosodium urate crystals, which are deposited in the joints, midfoot, and knees (Dalbeth *et al*., 2019) . It is a common inflammatory arthritis that is predominantly observed in men compared to women (Kuo *et al*., 2015). Few studies have investigated sex differences in gout, with most focusing more on men (Harrold *et al*., 2006). However, over the past few years, there has been a steady increase in the number of cases of gout among women. The manifestations of gout differ between men and women. In women, gout begins to manifest during old age and is accompanied by other comorbidities. Uric acid excretion levels are also lower in women than men (Veenstra *et al*., 2021). Studies on the association between gout and dementia have yielded contradictory results. Most observational studies, including population-based studies, have shown that gout is associated with a higher risk of dementia and cognitive impairment, whereas others have shown its association with a lower risk of dementia (Singh and Cleveland, 2018a).

HMG-CoA reductase (HMG-CoA) inhibitors (statins): Statins or 3-HMG-CoA inhibitors are commonly prescribed to individuals with CVDs because of their lipid-lowering characteristics, especially patients with IHD (Kuwabara *et al*., 2016). Statins target hepatocytes by inhibiting HMG-CoA, a major regulator of cholesterol biosynthesis. A reduction in intracellular cholesterol production results in an increase in low-density lipoprotein receptors in the liver, thereby reducing circulating low-density lipoprotein levels (Vaughan *et al*., 2000). Women treated with statins display remarkably increased high-density lipoprotein cholesterol concentrations compared with men; however, no sex differences were observed in other lipid parameters (Giannopoulos *et al*., 2012). The possible mechanism by which statins protect against dementia is through an anti-inflammatory effect involving endothelial nitric oxide synthesis, a process crucial for improving neurovascular dysfunction. Additionally, the modulation of lipoprotein oxidation is thought to be linked to AD (Poly *et al*., 2020). Several statins are currently prescribed; the most frequently prescribed are atorvastatin, simvastatin, rosuvastatin, pitavastatin, pravastatin, fluvastatin, and lovastatin (Kim *et al*., 2020). Long-term treatment (≥1 year) with statins such as atorvastatin, rosuvastatin, pitavastatin, pravastatin, and fluvastatin tends to be protective against new-onset dementia. Among these, rosuvastatin is the most effective in preventing dementia. The effects of statins differ by sex. Atorvastatin, rosuvastatin, and pravastatin significantly affect men, whereas rosuvastatin, pravastatin, and lovastatin are more effective in women. In contrast, short-term treatment with atorvastatin or simvastatin increases the risk of dementia (Kim *et al*., 2020). Epidemiological studies have also shown a remarkable reduction in cholesterol levels in women compared to men following the use of statins. Therefore, sex differences in clearance, bioavailability, and clinical outcomes may exist. However, the underlying cause of these sex-related differences remains unclear.

α-glucosidase inhibitor (acarbose): One of the prescribed medications for the treatment of T2D is acarbose, an α-glucosidase inhibitor. Acarbose acts by inhibiting the α-glucosidase enzyme that is involved in the hydrolysis of oligosaccharides and polysaccharides to monosaccharides in the brush border of the gut epithelium (Derosa and Maffioli, 2012). Inhibition of α-glucosidase delays the digestion of carbohydrates and absorption of glucose, leading to improved postprandial glucose control and increased serum levels of glucagon-like peptide-1 (GLP-1) to a controlled glycemic level (Hsu *et al*., 2018). However, no studies have reported sex differences in the effects of acarbose on T2D. In an investigation using Taiwan's National Health Insurance database, patients who underwent acarbose therapy for T2D were found to have a decreased risk of incident dementia (Tseng, 2020). Acarbose can potentially reduce the risk of dementia by lowering postprandial glucose levels, accompanied by a low risk of hypoglycemia, improved insulin resistance, improved lipid profiles, and increased serum GLP-1 levels. Although acarbose and its metabolites do not cross the blood-brain barrier (Harrison *et al*., 2014), they exert protective effects through their antioxidant and anti-inflammatory activities, improve lipid profiles, inactivate platelets, and reduce glucose levels, leading to a decreased risk of dementia (DiNicolantonio *et al*., 2015). A beneficial effect in women and a neutral effect in men have been observed (Tseng, 2020). Additionally, individuals who used acarbose, metformin, and pioglitazone benefited from the combined effect of a decreased incidence of dementia (Tseng, 2020).

Incretin mimetics (exenatide): Exenatide is a GLP-1 receptor agonist that stimulates GLP-1 receptors to cause glucose-dependent enhanced insulin secretion, suppression of glucagon secretion, and reduction in food intake (Wang *et al*., 2022). The observed weight-loss effect of exenatide is more prominent in women than in men, although no difference is found in glycemic control between the two sexes (Pencek *et al*., 2012). Exenatide is the drug of choice for patients who are overweight and suffer from T2D, with women experiencing a more beneficial effect than men (Klonoff *et al*., 2008). Exenatide can cross the blood-brain barrier and bind to GLP-1 receptors in various brain regions, exerting its protective effects through different signal transduction pathways (Wang *et al*., 2022). *In vivo* and *in vitro* studies have shown that exenatide shows neuroprotective action against neuronal cell death and oxidative stress and decreases Aβ levels (Perry and Greig, 2005). In addition to improving learning and memory, it promotes neurogenesis and synaptic plasticity (Mullins *et al*., 2019). A correlation was found between the use of exenatide and the incidence of dementia, and among all participants, the incidence of dementia was lowest in intensive users compared to that in non-users and non-intensive users. Participants with T2D who used exenatide showed remarkably reduced AD; specifically, a strong association was found in women (Zhou *et al*., 2021).

Biguanides (metformin): Metformin is currently used as a first-line treatment for T2D. It reduces hepatic gluconeogenesis and increases glucose uptake in the muscle by activating

5'-adenosine monophosphate-activated protein kinase, thereby reducing blood glucose levels (Rena *et al*., 2013). Women are commonly prescribed metformin because of its effects on weight loss, improvement in blood pressure and cholesterol levels, and regulation of insulin resistance (de Vries *et al*., 2020). Moreover, remarkably improved insulin secretion was observed in women treated with metformin, whereas no notable changes were observed in men (Li *et al*., 2021). Because metformin accumulates through the blood-brain barrier, it can activate adenosine monophosphate-activated protein kinase and exert anti-inflammatory effects in peripheral tissues as well as in the brain. Metformin exerts neuroprotective effects against oxidative stress-induced neuronal cell death (Ng *et al*., 2014). Samaras *et al*., (2020) reported that diabetic and non-diabetic participants taking metformin showed a similar decline in cognitive function, with the rate of cognitive decline being much faster in diabetic subjects not taking metformin (Samaras *et al*., 2020). Thus, in patients with diabetes, the risk of dementia was reduced by 81% in those who used metformin compared with those who did not. In women, overall cognitive and executive functions decreased more significantly in non-users than in metformin users.

PPAR-γ agonist (pioglitazone): Thiazolidinediones are agonists of the nuclear receptor peroxisome proliferator-activated receptor gamma that are prescribed as therapeutics for T2D and insulin resistance (Chou *et al*., 2017). Pioglitazone, a thiazolidinedione, interacts with the peroxisome proliferator-activated receptor, which modulates various cellular activities, including insulin regulation. Pioglitazone reduces insulin resistance by lowering glucose levels and preserving pancreatic B-cells (Campbell, 2004). Studies suggest that pioglitazone may be more effective in women than in men, while the majority of large-scale studies have not reported any sex differences (Benz *et al*., 2012). The observed differences may be due to the pharmacokinetic differences between men and women, leading to higher plasma levels of CRP and leptin in women than in men (Esteghamati *et al*., 2013). Peroxisome proliferator-activated receptor gamma can potentially improve cognition in AD through several mechanisms, such as exhibiting an anti-inflammatory effect (Combs *et al*., 2001), improving synaptic plasticity and mitochondrial function (Colca *et al*., 2014), reducing tau pathology, and reducing Aβ levels by enhancing Aβ clearance (Chen *et al*., 2015). Therefore, thiazolidinediones can serve as therapeutic candidates for AD. In a large cohort trial, the dementia-preventive effect of pioglitazone varied with the cumulative dose, duration of treatment, and average daily dose. People who took pioglitazone at high doses or for a long period had a significantly reduced risk of dementia compared to those who took the drug at low doses or for a short period. Therefore, the use of pioglitazone in individuals with diabetes can effectively prevent dementia in time- and dose-dependent manners (Chou *et al*., 2017). Furthermore, a recent study observed a reduced risk of incident dementia in patients taking thiazolidinediones, especially pioglitazone, which offers a better neuroprotective effect than other antidiabetic drugs independent of age and sex (Lu *et al*., 2018). However, further clinical trials are required to confirm and assess the sex-specific neuroprotective effects of this drug.

Incretin mimetics (liraglutide): Liraglutide, a GLP-1 receptor agonist, is used to treat type T2D and obesity (Norgaard *et al*., 2022). It improves blood glucose levels and causes satiety, leading to weight loss (Santilli *et al*., 2017). The inhibition of neuropeptide Y and agouti-related peptides and the activation of proopiomelanocortin neurons cause reduced food intake and fullness (Secher *et al*., 2014). The action of this drug can also be linked to other brain areas, such as the mesolimbic system, which leads to a decrease in food-induced reward signals and food-seeking behavior (Dickson *et al*., 2012). Undoubtedly, liraglutide is effective in reducing weight, with accumulating evidence from different studies suggesting that the effect of liraglutide is more evident in women (32%) than in men (Overgaard *et al*., 2016). Although the underlying mechanism for this better response in women is unclear, it could be related to increased drug exposure due to their low body mass index (Onishi *et al*., 2017). Liraglutide exerts its action peripherally, crosses the blood-brain barrier, and prevents or reverses memory impairment, as shown by *in vivo* studies (Crane and McGowan, 2016). Additionally, it increases the expression of GLP-1R in the hippocampus, thereby improving cognitive functioning through decreased Aβ-stimulated tau hyperphosphorylation caused by the stimulation of AKT and inhibition of glycogen synthase kinase-3β (Batista *et al*., 2018). A randomized controlled study using a parallel-arm design showed that the liraglutide arm was linked to improvements in the memory domain and short-term memory. However, instead of time-to-weight loss, an improvement was observed in the duration of drug exposure (Vadini *et al*., 2020). Therefore, although sex-specific data to maximize the use of liraglutide for the management of AD are lacking, treatment duration may be associated with improved memory (Vadini *et al*., 2020).

Xanthine oxidase inhibitor: Two types of xanthine oxidase inhibitors are used to treat gout: allopurinol and febuxostat. Allopurinol is a purine analog that non-selectively inhibits the xanthine oxidoreductase system, which is responsible for converting hypoxanthine into xanthine and xanthine into uric acid, leading to the formation of superoxide species that increase oxidative stress. In contrast, febuxostat is a non-purine analog that selectively inhibits the xanthine oxidoreductase system (Singh and Cleveland, 2018a). Febuxostat is well tolerated by both men and women of different ages. There are no significant age- or sex differences in the pharmacokinetics, pharmacodynamics, or safety of febuxostat. Thus, dose adjustments are not required (Khosravan *et al*., 2008). Consequently, hyperuricemia may be associated with oxidative stress, which is implicated in the pathogenesis of dementia (Singh and Cleveland, 2018b). Therefore, allopurinol and febuxostat may reduce the risk of dementia by inhibiting the xanthine oxidoreductase system and reducing UA production of uric acid. The use of higher doses of allopurinol and febuxostat (40 mg/day) correlates with a reduced risk of incident dementia compared to the use of a lower amount of allopurinol (<200 mg/day); however, the duration of treatment is not associated with a reduced risk of incident dementia. Febuxostat did not show any significant difference in reducing the risk of dementia compared with allopurinol (Singh and Cleveland, 2018c). However, in this study, no sex differences were observed in the effects of allopurinol and febuxostat on reducing the risk of dementia (Veenstra *et al*., 2021).

Uricosuric drug: benzbromarone is used to treat hyperuricemia, a condition characterized by high levels of uric acid in the blood. It works by suppressing the resorption of uric acid through the inhibition of urate transporter 1 (Miao *et al*., 2008). A higher dose of benzbromarone is associated with a higher likelihood of successful therapeutics for gout. The rate

of the first gout flare was lower in the benzbromarone-treated group of both sexes, indicating no sex-specific difference in the effect of medications (Lai *et al*., 2022). Accordingly, the potent effect of benzbromarone on reducing uric acid levels and preventing acute gout attacks may be the underlying mechanism for its protective effect against incident dementia. Benzbromarone use significantly decreases the risk in individuals with dementia (73.7%). These findings suggest that the longer the duration of benzbromarone use, the lower the risk of dementia in both men and women. However, a significant decrease was observed only after 180 d of use. Furthermore, the neuroprotective effects of benzbromarone are more noticeable in men than in women (Chuang *et al*., 2020).

CONCLUSIONS

Currently, dementia treatments suffer from limitations and challenges in achieving a fundamental cure; therefore, preventing the onset of dementia can be an alternative strategy to reduce the incidence of dementia. As described in this review, there are significant sex differences in the impact of therapeutics targeting cardiovascular and metabolic diseases, which are risk factors for dementia, on the incidence of dementia. Men and women have different characteristics concerning specific drug pharmacokinetics and pharmacodynamics owing to genetic, hormonal, and structural differences in the brain. Therefore, it is essential to understand sex-specific differences in drug responses, as they may affect drug safety and effectiveness. Although many clinical studies include both men and women, most have not considered or analyzed sex/gender issues separately. Therefore, we suggest that clinical studies need appropriate sample sizes to separately test and analyze therapeutic efficacy in men and women. Furthermore, the risk of developing dementia is strongly dependent on age; thus, it would be desirable to correct sex differences in therapeutic effects depending on age. However, few studies on age-dependent differences in therapeutic effectiveness are available. In conclusion, this review suggests that future studies of dementia and its risk factors should consider sex- and age-related differences.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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