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Sex Differences in Cardiovascular Risk Factors for Dementia

Mi-Young Kim[1,†], Kyeongjin Kim[1,†], Chang Hyung Hong[2,3], Sang Yoon Lee[4] and Yi-Sook Jung[1,5,*]

[1]*College of Pharmacy, Ajou University, Suwon 16499,*
[2]*Department of Psychiatry, Ajou University School of Medicine, Suwon 16499,*
[3]*Institute on Aging, Ajou University Medical Center, Suwon 16499,*
[4]*Department of Biomedical Sciences, Chronic Inflammatory Disease Research Center, Ajou University School of Medicine, Suwon 16499,*
[5]*Research Institute of Pharmaceutical Sciences and Technology, Ajou University, Suwon 16499, Republic of Korea*

Abstract

Dementia, characterized by a progressive cognitive decline and a cumulative inability to behave independently, is highly associated with other diseases. Various cardiovascular disorders, such as coronary artery disease and atrial fibrillation, are well-known risk factors for dementia. Currently, increasing evidence suggests that sex factors may play an important role in the pathogenesis of diseases, including cardiovascular disease and dementia. Recent studies show that nearly two-thirds of patients diagnosed with Alzheimer's disease are women; however, the incidence difference between men and women remains vague. Therefore, studies are needed to investigate sex-specific differences, which can help understand the pathophysiology of dementia and identify potential therapeutic targets for both sexes. In the present review, we summarize sex differences in the prevalence and incidence of dementia by subtypes. This review also describes sex differences in the risk factors of dementia and examines the impact of risk factors on the incidence of dementia in both sexes.

Key Words: Sex difference, Dementia incidence, Dementia prevalence, Cardiovascular risk factors

INTRODUCTION

Dementia is a chronic, progressive, and multifactorial neurodegenerative disorder characterized by cognitive decline. It has been a major public health problem, with 36 million people worldwide estimated to have dementia, and the global prevalence of dementia is expected to increase to more than 80 million by 2040 (Ferri *et al*., 2005). In addition to the substantial burden on patients and their families, dementia also affects the healthcare system worldwide. As a result, the high demand for medical care and treatment need for cumulative cognitive decline will have significant socioeconomic impacts.

Dementia has been demonstrated to be highly related to various risk factors, including age and many diseases. For example, various cardiovascular disorders (CVD), such as atrial fibrillation (AF) (Ott *et al*., 1997), heart failure (HF) (Qiu *et al*., 2006), and hypertension (HTN) (Kivipelto *et al*., 2001), are well–known risk factors for dementia; therefore, prevention of these diseases can help reduce the burden of dementia on people and the healthcare system (Wu *et al*., 2016). In fact, several cardiovascular (CV) drugs have been reported to reduce the risk of dementia (Kim *et al*., 2016; Mangmool *et al*., 2017; Xiao *et al*., 2017).

Increasing evidence indicates that sex factors can play an important role in the pathogenesis of diseases, including CVD and dementia. According to recent reports, almost two-thirds of patients with Alzheimer's disease (AD), the most common type of dementia, are women (Hebert *et al*., 2013). However, the incidence studies suggest that sex differences in AD are still controversial. The Cache County Study in the United States (US) indicates a greater incidence of AD in men than in women before age 78, after which men have a lower incidence than women (Lethbridge *et al*., 2013). Notably, sex differences in the incidence of AD are not observed in most studies conducted in the US (Kukull *et al*., 2002). Therefore, it is critical to understand sex-related differences in the incidence of dementia, and the results would help to delineate the pathophysiology of dementia and suggest potential therapeutic strategies for men and women.

In this review, we discuss sex differences in the prevalence

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***Corresponding Author**
E-mail: yisjung@ajou.ac.kr
Tel: +82-31-219-3501, Fax: +82-31-219-3435
[†]The first two authors contributed equally to this work.

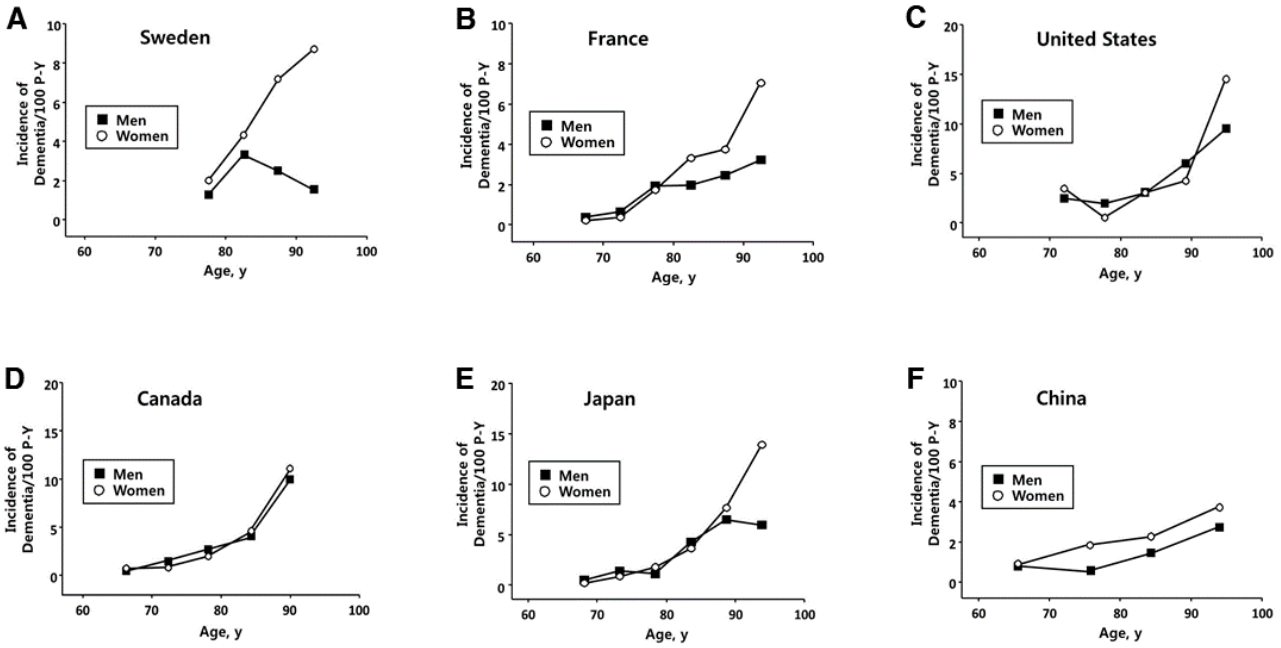

Fig. 1. Age- and sex-specific incidence/100 person-years of dementia in (A) Sweden (Fratiglioni *et al*., 1997), (B) France (Fratiglioni *et al*., 1997), (C) the United States (Katz *et al*., 2012), (D) Canada (The Canadian Study of Health and Aging Working Group, 2000), (E) Japan (Yamada *et al*., 2008), and (F) China (Chen *et al*., 2011).

and/or incidence of different subtypes of dementia. Sex differences in various CVDs, well-known risk factors for dementia, are also summarized. In addition, we review the impact of risk factors on the incidence of dementia in men and women.

DEMENTIA IN MEN AND WOMEN

Incidence and prevalence are common terms used to describe disease epidemiology. In medicine, the incidence is generally the case for newly identified diseases and the frequency of disease is the actual number of cases alive. Thus, to explain the etiology of disease, incidence is more usually used than prevalence. The prevalence of AD has been shown to be significantly higher in women than in men (Mielke *et al*., 2014). The Italian Cohort study on dementia indicates that women account for more than 70% in a total of 213 consecutive dementia patients (Musicco, 2009). However, this clinical observation cannot be simply interpreted as a high dementia risk in women because the prevalence is determined by both the incidence of disease and the post-onset survival duration (Hebert *et al*., 2003). Despite the well-known great prevalence of AD in women, epidemiologic studies examining the incidence of AD suggest a different result of sex differences. Sex differences in the incidence of dementia seem to be complicated because many diseases can cause dementia (Musicco, 2009). Thus, although some subtypes of dementia may occur more frequently in women, the sex differences may not always apply to AD. In addition, the prevalence can increase as a function of disease duration. Indeed, AD is a long-lasting disease, and many patients die from other causes during illness. Because the average life expectancy is longer in women than in men, more women, especially at the older ages, survive with AD. Therefore, sex-specific risks of dementia should be considered from the studies that focus on incidence but not on prevalence.

Many incidence studies carried out in Europe and the US are available in the scientific literature. Most of these studies have analyzed small populations, and the findings of sex differences show considerable variability. One large meta-analysis demonstrates that the risk of AD increases 1.6-fold in women (Gao *et al*., 1998), but the results have not been confirmed in recent US studies, which indicate the same incidence in both sexes. Fig. 1 shows the age- and sex-specific dementia incidence rates in studies in the US, Europe, and Asia. The incidence of dementia is higher in women especially aged more than 90 years in Europe and Japan. However, studies in the US and Canada show a little difference in the incidence between men and women. These results, although not well explained by methodological differences, suggest that some types of premorbid exposures, causally related to AD, and different patterns in various regions in the world may play different roles in both sexes.

Sex differences in prevalence also depend on dementia subtypes, such as AD, Lewy body dementia (LBD), vascular dementia (VD), and Parkinson's dementia (PD). For example, women have a higher risk of developing AD, and men have a higher risk of developing VD (Podcasy and Epperson, 2016). Table 1 summarizes the sex differences in prevalence/incidence of different subtypes of dementia. AD is shown to be the most common form of dementia, accounting for up to 60-80% of dementia cases. Progression of AD may be more rapid among elderly women, but studies from the US and the United Kingdom (UK) demonstrate that women with AD have a longer lifespan (Kua *et al*., 2014). Women are frequently diagnosed earlier with AD than men, which can determine their

Table 1. Effects of sex on prevalence/incidence of dementia subtypes

Subtypes of dementia	Sex differences in prevalence/incidence	References
Alzheimer disease (AD)	• Accounts for 60%-80% of dementia cases • Lifetime risk of AD in women is almost twice that of men • Men with AD have a shorter lifespan, regardless of age at diagnosis	Seshadri *et al*., 1997 Kua *et al*., 2014
Vascular dementia (VD)	• Accounts for 10%-20% of dementia cases • Risk factors for vascular or multi-infarct dementia • More common in males than in females; greater severity of impact in females than in males	Appelros *et al*., 2009 Pendlebury and Rothwell, 2009
Lewy body dementia (LBD)	• Extensive overlap with Parkinson disease dementia • Greater incidence in males than in females (4.8 vs 2.2) • More rapid cognitive decline in males than in females	Nelson *et al*., 2010 Savica *et al*., 2013
Parkinson disease dementia (PD)	• Higher prevalence in males than in females • Earlier onset of Parkinson disease dementia in males • Greater severity of cognitive decline in males	Elbaz *et al*., 2002 Gillies *et al*., 2014 Augustine *et al*., 2015
Due to multiple causes (mixed dementia)	• Prevalence differs greatly depending upon age and study but is 1.3% according to a recent systematic review • Almost twice as common in men as in women aged > 60, although other studies suggest equal frequency in males and females	Martin-Laez *et al*., 2016 Siraj, 2011
Creutzfeldt-Jakob disease (CJD)	• Rare: 1.26 cases/million people. • Sex differences in prevalence and clinical course have not been reported	Gubbels *et al*., 2012 Skillback *et al*., 2014

Modified from Podcasy and Epperson (2016).

postdiagnosis longevity. It is becoming increasingly important to consider sex together with other risk factors (such as apolipoprotein E genotype and depression) for dementia. The development of AD in women at a later age has been associated with a longer lifetime exposure to estrogens (Lin *et al*., 2011). However, women show a marked decrease in estradiol levels in the second half of menopause, while age-matched men retain either a lifelong gonadal steroid level or a relatively slower decline in testosterone synthesis (Mielke *et al*., 2014). VD is reported to account for 10-20% of dementia cases and results from hemorrhagic or ischemic insults in some regions of the brain, which is critical for cognitive functions (Gorelick *et al*., 2011). Studies conducted worldwide indicate that the prevalence of stroke, either ischemic or hemorrhagic stroke, is 44% higher in men than in women. However, other studies demonstrate that women have a greater risk for stroke possibly because of their longer life span and increased risk of thrombosis and stroke with AF (Cheng and Kong, 2016). LBD is clinically distinguished from Parkinson's dementia because the onset of dementia precedes the onset of parkinsonism. The pathology of LBD is known as an abnormal deposition of α-synuclein, known as Lewy body. Autopsy analysis of patients who died with dementia reveals that Lewy bodies are shown almost three times more often in men than in women, regardless of age, smoking, or education (Nelson *et al*., 2010). PD is a movement disorder characterized by tremor at rest, rigidity, and difficulty with speech, and loss of midbrain dopaminergic neurons in the substantia is known to be the main cause of disease. The prevalence of PD is known to be between 0.3% and 3% of the population worldwide and is 2 times higher in men than in women at any given age (Elbaz *et al*., 2002). Among individuals who are treated in the early stages of PD, women are better in cognitive functioning than men (Augustine *et al*., 2015). Dementia from multiple causes (mixed dementia) is referred as cognitive impairment due to multiple central nervous system pathologies, which are most often a combination of AD pathology, β-amyloid deposits, and vascular damage, such as multiple microbleeds or infarcts (Jellinger, 2013). According to autopsy reports, vascular damage occurs in up to 28% of AD cases (Gearing *et al*., 1995). Creutzfeldt-Jakob disease (CJD) primarily occurs in individuals aged more than 60 years worldwide. Although little is known about the pathophysiology of the disease, researchers believe that the disease is caused by prions or misfolded proteins, which aggregate in the brain and lead to neuronal death and progressive dementia. The cases of CJD do not vary by sex, and no differences in the survival time after diagnosis are observed between men and women (Gubbels *et al*., 2012).

SEX DIFFERENCES IN CARDIOVASCULAR RISK FACTORS FOR DEMENTIA

Various CV disorders, such as coronary artery disease (CAD), AF, myocardial infarction (MI), HF, and HTN are known risk factors for dementia. Table 2 presents sex differences in the prevalence and incidence of these CV disorders. In addition, as shown in Table 3, the sex differences in the impact of CV disorders on the incidence of dementia are discussed here.

Coronary artery disease

CAD usually results from atherosclerosis and causes chest pain, shortness of breath during exercise, and heart attack. According to data from National Health and Nutrition Examination Survey (NHANES) 2011 to 2014 (National Center for

Table 2. Sex differences in prevalence/incidence of cardiovascular diseases which are known as dementia risk factor

CV Risk factors	Sex differences in prevalence/incidence/prognosis	References
Coronary artery disease (CAD)	• Higher prevalence in males than in females for all ages • CAD first presents approximately 10 years later in women than in men, most commonly after menopause • More annual incidence of all coronary events in men than in women aged <65 years • Women with CAD have worse outcomes than their male counterparts	Bairey Merz *et al*., 2006 Shaw *et al*., 2006 Lerner and Kannel, 1986 Davis *et al*., 2015
Atrial fibrillation (AF)	• The age-adjusted prevalence of AF is reported to be higher in men • Higher incidence rates in males than in females. • Lifetime risk of developing AF is slightly lower in women than in men • Mortality associated with AF is higher in females overall	Chugh *et al*., 2014 Heeringa *et al*., 2006 Svennberg *et al*., 2015 Piccini *et al*., 2012
Myocardial infarction (MI)	• Lower incidence rate in women than in men, except among very old people (≥95 years), • By age groups, males have a higher prevalence of MI than females • Men have roughly twice the risk of MI compared with women • Women have been found to have worse short-term prognosis than men	Albrektsen *et al*., 2016 de Torbal *et al*., 2006 Benjamin *et al*., 2018 Malacrida *et al*., 1998
Heart failure (HF)	• Prevalence is higher in men than in women • Incidence rates are on average approximately two times higher in men than in women in each age category • Women are found to have a lower mortality than men	Bleumink *et al*., 2004 Adams *et al*., 1996 Burns *et al*., 1997
Hypertension (HTN)	• HTN prevalence tends to be higher in women • During early adulthood, women have lower systolic BP than men, but after the age of 60 years, the opposite is the case • Even though BP control improves with time in women and men, fewer women than men have controlled BP levels despite treatment	Roger *et al*., 2011 Ostchega *et al*., 2008 Lloyd-Jones *et al*., 2005

IR: incident rate, BP: blood pressure.

Health statistics) in the US, the prevalence of CAD is higher in men than in women for all ages, 7.4% for men and 5.3% for women (Kivipelto *et al*., 2001). However, women with CAD show worse outcomes than men do when no adjustments are made for other characteristics and comorbidities. Women tend to present with CAD in life, and even in the young ages, they tend to have less evidence-based treatment for CAD than men do (Davis *et al*., 2015). CAD first presents approximately 10 years later in women than in men possibly because of the protective effect of estrogen. Upon reaching menopause, the incidence of CAD in women catches up with that in men (Yusuf *et al*., 2001).

The differences in CAD between women and men have been explained particularly by focusing on estrogen (Lawton, 2011). Estrogen is thought to be beneficial through vasodilation and the protective effects against atherosclerotic plaque, oxidative stress, and inflammation (Mendelsohn and Karas, 2005). Animal models have suggested that benefits conferred to females are due to estrogen (Patten *et al*., 2004). However, the cardiovascular advantages of exogenous estrogen have not been demonstrated clinically. Large randomized studies have reported that the estrogen treatment in postmenopausal women is not beneficial and even potentially harmful (Grady *et al*., 2002). Another reason for the greater incidence of CAD in men is the fact that men have an increased burden of atheroma than women. A study suggests that rupture of atheroma plaque in patients with sudden death is more often in men than in women (Patten *et al*., 2004). Men have more severe structural and functional abnormalities in the epicardial coronary arteries than women. In addition to physiological differences, other factors may be contributable to the clinical differences between women and men with CAD.

A strong association has been reported between CAD and dementia. The incidence of dementia is higher in those with prevalent CAD in the Cardiovascular Health Study cohort in the US (Newman *et al*., 2005), and several studies have confirmed that CAD is associated with cognitive impairment (Roberts *et al*., 2010) and hippocampal damage (Koschack and Irle, 2005). Recent studies have shown that CAD is observed more frequently in VD patients (Graban *et al*., 2009) and that the damaged region of the brain is strongly related to the atherosclerotic burden. Microvascular lesions in the brain are considered an important pathophysiological mechanism by which CAD acts as a risk factor for dementia (Rosano *et al*., 2005). Microvascular lesions in the brain disturb cerebral blood flow (CBF) regulation and perfusion, reduce cerebral circulation through blood-brain barrier disruption, and finally lead to brain tissue damage (Kovacic *et al*., 2011). In addition, several recent studies have found that the failure to clear excess Aβ (produced in cortical neurons) in the blood-brain barrier network contributes to cerebral hemorrhaging and AD pathology (Bell and Zlokovic, 2009). These aforementioned studies indicate a correlation between the CAD history and low cognitive scores and suggest that the longer the CAD period, the lower the cognitive scores. In men, those who had the first CAD event 10 years ago are more likely to have poor

Table 3. Sex differences in the impact of cardiovascular risk factors on dementia incidence

Cardiovascular risk factors	Dementia risk		Note	References
	Men	Women		
Coronary artery disease (CAD)	+	+	Low cognitive scores in men and women (middle life)	Singh-Manoux *et al*., 2008
Atrial Fibrillation (AF)	+	+	Increased incidence of dementia in men and women	Chen *et al*., 2018 Miyasaka *et al*., 2007
Myocardial Infarction (MI)	+	N.S.	Increased incidence of dementia in men but not in women with unrecognized MI	Ikram *et al*., 2008
	+	++	Greater dementia risk in women than in men	Aronson *et al*., 1990
	+	+	Increased risk for vascular dementia but not for Alzheimer dementia in men and women	Sundboll *et al*., 2018
Heart failure (HF)	+	N.S.	Increased incidence of dementia in men but not in women	Noale *et al*., 2013
	+	+	Increased dementia risk in both men and women	Adelborg *et al*., 2017
Hypertension (HTN)				
All age	N.S.	+	Low cognitive scores in women but not in men	Arntzen *et al*., 2011
	+	+	Increased incidence of dementia in men and women	Israeli-Korn *et al*., 2010 Kimm *et al*., 2011
Mid-life	N.S.	+	Increased dementia risk in women but not in men	Gilsanz *et al*., 2017 Joas *et al*., 2012
Late- life	N.D.	N.S.	Risk for mild cognitive impairment or probable dementia is not significant in postmenopausal women	Johnson *et al*., 2008

+: increases dementia risk, ++: increases dementia risk to a great extent, N.D.: not mentioned, N.S.: not significant risk.

cognition. Therefore, future studies should be carried out to examine the correlation between the CAD history and cognition not only in men but also in postmenopausal women.

Atrial fibrillation

AF is the most common persistent cardiac arrhythmia and is recognized as one of the major public health problems (Naccarelli *et al*., 2009). Its prevalence is known to increase steadily with age, and the number of patients aged ≥65 is expected to reach 1.3 billion by 2040 worldwide (Dublin *et al*., 2011). The age-adjusted prevalence of AF is reported to be higher in men (10.3%) than in women (7.4%) in the US Medicare recipients (Piccini *et al*., 2012). Consistently, the incidence rates of AF are also shown to be higher in men than in women. Current evidence indicates that age and sex are the two most powerful predictors for the incidence of AF. In fact, the incidence of AF has been reported to be as high as 32.9 per 1,000 men and 30.4 per 1,000 women by age 85-89 years (Wilke *et al*., 2013). The lifetime risk of AF incidence has been slightly higher in men than in women (23.8% vs. 22.2% at 55 years of age in the Rotterdam study and 25.8% vs. 23.4% at 60 years of age in the Framingham study) (Lloyd-Jones *et al*., 2004). In addition, data from California administrative databases were analyzed for racial variation in the incidence of AF. After adjustment for AF risk factors, lower incidence rates have been found in blacks (Hazard Ratio (HR), 0.84; 95% Confidence Interval (CI), 0.82-0.85; $p<0.001$), Asians (HR, 0.78; 95% CI, 0.77-0.79; $p<0.001$), and Hispanics (HR, 0.78; 95% CI, 0.77-0.79; $p<0.001$) than in their white counterparts (Dewland *et al*., 2013). However, despite the high prevalence, incidence, and risk for AF in men, the count of women with AF is greater than that of men with AF due to the differences in life expectancy. In addition, the relative mortality rate of AF patients has been higher in women than in men. Although the findings in individual studies are still controversial, a meta-analysis study has demonstrated that the pooled ratio of relative risks for AF-associated all-cause mortality is 12% higher in women than in men (HR 1.12; 95% CI, 1.07-1.17) (Emdin *et al*., 2016).

The precise mechanisms that cause sex-related differences in AF are poorly explained, but several suggestions have been proposed. First, anthropomorphic differences (especially in lean body weight) between men and women cause a larger size and volume of left atrium in men than in women, and the changes could promote AF-maintenance, independently of the increase in AF incidence (Liu *et al*., 2004). Second, women with AF have a relatively greater burden of atrial fibrosis (Cochet *et al*., 2015). Third, variations in the X-linked genes may account for some sex differences in AF (Ravn *et al*., 2005). Further basic and clinical research are needed to clarify the pathophysiological aspect of sex differences in AF. In fact, the contribution of sex hormones has been examined in several studies. Testosterone deficiency has been shown to increase arrhythmogenicity possibly through increased calcium release from the sarcoplasmic reticulum, and this abnormality is reversed by testosterone therapy in an animal study using mice (Tsuneda *et al*., 2009). Clinically, it is observed that an increased risk of AF is associated with decreased testosterone levels in men (Magnani *et al*., 2014).

Recently, increasing evidence suggests that patients with AF have been associated with not only high rates of CAD and

HF but also an increased risk of cognitive decline (Dublin *et al*., 2011). A meta-analysis study of eight studies including 77,668 patients has demonstrated that AF significantly increases the risk of dementia incidence by 42% (Santangeli *et al*., 2012). In addition, AF possibly causes modifiable ischemic stroke and leads to considerable physical and cognitive disability and dementia (Alonso and Arenas de Larriva, 2016). The relationship between AF and dementia in the absence of stroke is still uncertain (Kwok *et al*., 2011), but it is clear that AF can cause the onset of dementia (Barba *et al*., 2000; Rastas *et al*., 2007). Moreover, growing evidence supports AF as a risk factor for dementia without stroke (O'Connell *et al*., 1998). In fact, several studies have shown that AF is associated with brain abnormalities, more specifically, a small hippocampal volume and left ventricular hypertrophy (Wozakowska-Kaplon *et al*., 2009). Individuals suffering from AF also show poor learning, memory, attention, and performance (Knecht *et al*., 2008), as well as decreased scores on cognition tests (Schrader, 2004; Kermode-Scott, 2012).

Several mechanisms have been suggested to link AF and dementia. In AF patients, irregular rapid ventricular rates may cause a reduced cerebral perfusion because of low cardiac release (Petersen *et al*., 1989; Duron and Hanon, 2010). Another suggested mechanism is the increased risk of covert cerebral infarction and transient ischemic attack (Ezekowitz *et al*., 1995; Vermeer *et al*., 2003). AF can also result in a hypercoagulable state, which may give rise to subclinical cerebral embolism (Choudhury and Lip, 2003; Barber *et al*., 2004). Furthermore, cerebrovascular disease may precipitate neurodegenerative changes, manifesting as white matter hyperintensities on MRI (Kalaria, 2000). A recent study of sex differences in the relationship between AF and dementia suggests that age-adjusted rates of dementia are not different between men and women with AF (Miyasaka *et al*., 2007). Another sex-stratified analysis indicates that the risk of dementia associated with AF in women is comparable with that in men (p=0.96 for interaction by sex) (Chen *et al*., 2018). Therefore, further studies should focus on the sex differences in the relationship between AF and dementia.

Myocardial infarction

MI is defined as cardiomyocyte necrosis because of the sustained ischemia/hypoxia. It is frequently, but not always, an acute manifestation of atherosclerosis-related CAD (Mendis *et al*., 2011). Based on a UK national survey of self-reported MI, the prevalence of MI is approximately 4.1% in men and 1.7% in women in 2006, and the prevalence is age-dependent, extending from 1% in men aged <45 years to 17% in those aged ≥75 years. Similarly, the overall prevalence of MI is 3.0% in US adults aged ≥20 years according to data from NHANES 2011 to 2014. Men have a higher prevalence of MI than women in all age groups except those of 20 to 39 years (3.8% for men and 2.3% for women), and more women than men have MI in the highest age group because of women's longevity (Benjamin *et al*., 2018). The sex difference in the risk of MI persists throughout life; the relative risk of MI diminishes with age, but the absolute sex differences increase (Albrektsen *et al*., 2016). The lower risk in women at premenopausal ages may be associated with a beneficial effect of female hormones on vascular function, lipid profile, or other cardioprotective molecules (Chou and Saw, 2014). Despite a positive role of female hormones on CV risk factors, a few previous studies have reported no or even an adverse effect of hormone treatment on the risk of MI (Coutinho, 2014). Actually, it is not easy to distinguish between effects of age and menopause (Gierach *et al*., 2006), but the age-incidence relationship with hormone-dependent diseases may be affected by hormone changes (Kalin and Zumoff, 1990). However, once a woman has MI, she loses the advantage and may become no better or worse than a man with MI at the same age (Rosengren *et al*., 2001). It is still controversial about the prognosis of women with MI. Several studies (Greenland *et al*., 1991; Maynard *et al*., 1992) indicate that women have a worse short-term prognosis than men; however, in general, the findings have been partly attributed to differences in age and prion diseases, mainly diabetes.

It is a growing interest to define the mechanism underlying the sex-related differences in MI-associated damage, but conflicting results have been found. Ischemic insults in the heart reduce blood flow and trigger apoptotic death, and loss of cardiac cells results in tissue damage. A primary clinical strategy is to restore blood flow, although the restored blood flow may further increase tissue damage because of myocardial ischemia/reperfusion (I/R) injury. An animal study has found that regional myocardial I/R in the heart produces a significantly larger size of infarct in male rats than in female rats (Le *et al*., 2014). Aggravated reperfusion injury correlates with increased apoptosis in the area at risk, and consistent with the smaller infarct size, significantly less apoptosis is observed in the female heart. In fact, testosterone has been shown to inversely affect myocardial remodeling after MI (Kanashiro-Takeuchi *et al*., 2009). Testosterone is known to activate nuclear factor-kB, which contributes to inflammatory mechanisms and the downregulation of fatty acid oxidation (Gardner *et al*., 2002).

Only a limited number of studies have examined the relationship between MI and dementia. Patients with MI have been shown to share a genetic background, including abnormal cholesterol metabolism and upregulated inflammation, with those with AD. Some studies have revealed a high risk of cognitive impairment after MI because of brain hypoperfusion (Zuccala *et al*., 2001), and a cross-sectional evaluation in the Rotterdam study reveals a positive relationship between MI and cognitive impairment and (Breteler *et al*., 1994). In addition, the Bronx Aging Study suggests that women with a history of MI have a 5-fold increase in the risk of dementia (Aronson *et al*., 1990). Another study indicates that the incidence of dementia is remarkably higher in women with than without a history of MI, but the results are not found in men (Aronson *et al*., 1990). The significant findings suggest that women with MI may be particularly susceptible for dementia (Aronson *et al*., 1990). However, the impact of MI on dementia remains controversial; for example, the Honolulu-Asia Aging Study has not demonstrated a link between later cognitive impairment and MI (Petrovitch *et al*., 1998). Therefore, further studies remain to improve understanding of the effect of MI on dementia.

Heart failure

HF is defined as "a complex clinical syndrome that can result from structural or functional heart injury that reduces the ability of the ventricle to pump blood" (Hunt *et al*., 2005). Because HF is a syndrome rather than a disease, the diagnosis can depend on a clinical test. The incidence of HF has been reported to be 14.4/1000 person-years (95% CI, 13.4-15.5) and is significantly higher in men (17.6/1000 man-years; 95% CI, 15.8-19.5) than in women (12.5/1000 woman-years; 95%

CI, 11.3-13.8) (Bleumink *et al*., 2004). The incidence rate increases with age from 1.4/1000 person-years in those aged 55-59 years to 47.4/1000 person-years in those aged 90 years or older, and the age-associated increase is shown to be evident for both sexes. A Portugal study indicates that HF incidence per year is 1.3 cases per 1,000 people aged over 25 years, 8.8 cases per 1,000 people aged over 65 years, and 11.6 cases per 1,000 people aged over 85 years, and males have a 1.75-fold higher rate than females (Ceia *et al*., 2002). However, in the UK, the overall HF incidence rate per year is 4.4 cases per 1,000 people in men and 3.9 cases per 1,000 people in women and doubles every 5 years after the age of 55 years (Johansson *et al*., 2001).

HF seems to have different characteristics in men and women. Some of the differences are attributed to age, ventricular function, and causes of HF. Women have a higher onset age of HF and have HF more often without left ventricular systolic dysfunction but less often due to ischemic heart disease than men. In addition to these effects, a pathophysiological specificity for sex is also observed. Left ventricular responses to pressure overload conditions, such as hypertension, can be modified by sex, and women are less likely to have ventricular dilatation (Mendes *et al*., 1997; Luchner *et al*., 2002). The relationships between hormones and the renin-angiotensin system are identified and may contribute to differences in remodeling, and the ventricular dilatation progresses less intensely in women (Fischer *et al*., 2002). Women have a great baseline activity of the vasodilator natriuretic peptide system, the fact that can contribute to the protective role. In contrast, women have increased the stiffness of vessel and ventricle even in the absence of heart disease (Redfield *et al*., 2005), and the combined ventricular–vascular stiffening may contribute to the increased prevalence of HF in women. Furthermore, women also tend to be more depressed than men do. Therefore, they have a lower threshold for perceiving and expressing their symptoms. In addition, social integration, another psychosocial factor, affects C-reactive protein concentration, a measure of inflammatory activation, in men but not in women (Ford *et al*., 2006). Thus, men tend to develop silent biological responses to such stimuli, and the responses may indirectly affect the cardiovascular risk. Therefore, clinical trials in women or at least with enough women are needed to guide management of HF.

The Heart-Mind Study suggests that participants with HF experience declines in cognitive function (Almeida *et al*., 2012). In addition, other studies demonstrate that HF is associated with both cognitive impairment and dementia (Trojano *et al*., 2003). A recent pilot case-control study indicates that HF patients have lower scores in cognitive functions, including visuospatial and executive function, visual memory, and verbal learning tasks (Beer *et al*., 2009). Investigation for pathophysiological mechanisms underlying the relationship between HF and dementia are still on going. Reduced CBF appears to worsen cognitive impairment related with HF, and those with heart transplantation have restored CBF and improved cognitive performance (Gruhn *et al*., 2001; Alves *et al*., 2005). In HF, low cardiac output combined with impaired cerebral autoregulatory systems may lead to reduced CBF and increased cognitive impairment and dementia (Jefferson *et al*., 2007, 2010). HF is also a risk factor for multiple cerebral emboli, which could cause cognitive impairment (Pullicino and Hart, 2001). HF is demonstrated to be a remarkable risk factor for dementia incidence in men (HR=2.58, 95% CI=1.11-5.99) but not in women (Noale *et al*., 2013). However, another study suggests that HF is a risk factor for dementia in both men and women, and slightly greater HR is found in men (HR=1.31; 95% CI, 1.26-1.36) than in women (HR=1.15; 95% CI, 1.11-1.18) (Adelborg *et al*., 2017). Although causes and outcomes of HF can differ between men and women (Taylor, 2015), the basis of the sex differences in the dementia risk is still unclear.

Hypertension

HTN is defined as a systolic blood pressure (BP) of 140 mmHg or a diastolic BP of 90 mmHg, and it has been reported that approximately 80 million US adults more than 20 years old have HTN (i.e., 32.6% prevalence) (Mozaffarian *et al*., 2016). HTN prevalence is shown to be the highest in non-Hispanic Blacks (33.5%), and it increases with age (65.4% among those aged ≥60 years) and tends to be higher in women than in men. The numbers of patients treated for HTN increase with time in both women and men and are more in women than in men. Although BP control has improved over time in women and men, fewer women than men have been able to control BP despite treatment, especially in the elderly. HTN is also more prevalent in women among the elderly (Roger *et al*., 2011), and about 80% of women aged over 70 years suffer from HTN (Roger *et al*., 2011). Women have a lower systolic blood pressure than men in early adulthood, but this trend is reversed after age 60 (Lloyd-Jones *et al*., 2005). Decreased survival in old hypertensive men can account for the higher prevalence of HTN in old women. Diastolic BP is slightly lower in women than in men, regardless of age. The prevalence of hypertension is significantly higher in men than in men (34% and 22%, respectively) (Ostchega *et al*., 2008). Previous NHANES data reveal a minimal difference in HTN incidence between women and men at all ages, but the incidence of HTN in black is almost twice that of white for almost all age- and sex-matched groups (Cornoni-Huntley *et al*., 1989). In the subgroup of adults under age 60, women (87%) are more likely to recognize and seek treatment for HTN than men (63%) (Ostchega *et al*., 2008). No differences in perception of HTN are found between hypertensive men (84%) and women (81%) over 60 years of age. Among HTN patients aged 18-59 years, men (47%) are less likely to be treated than women (74%), but no differences in treatment are observed between hypertensive men (78%) and women (75%) aged 60 years and older (Engberding and Wenger, 2012).

High BP is a well-known risk factor for cerebrovascular disorders, including cerebral infarct, stroke, and dementia (Vermeer *et al*., 2003; Celle *et al*., 2012). However, whether HTN is an independent risk factor for dementia is unknown. The association between HTN and the risk of dementia is prominent, and few studies have failed to show this relationship (Johnson *et al*., 2008). The high prevalence of HTN at the age of between 30 and 50 years indicates that understanding the relationship between HTN and dementia is important for the potential prevention of dementia. In fact, the Cache County study by Mielke *et al*. also indicates that systolic BP of 160 mmHg is related with greater rates of cognitive decline in the elderly than low systolic BP. Other studies have further shown that HTN is associated with not only VD but also AD (Staessen *et al*., 2007). In particular, elderly people with HTN rather than young people with HTN are shown to have an increased risk of VD (Yamada *et al*., 2003). The relationship between HTN

and risk of AD has been also suggested by a recent study, which demonstrates a significant interaction between diastolic BP and plasma Aβ levels (Shah *et al*., 2012). In addition, mid-adulthood HTN is associated with increased dementia risk in women but not in men. It is predicted that women with onset HTN in the mid-adulthood have a 73% higher dementia risk than stable normotensive women (Gilsanz *et al*., 2017), but no evidence indicates that HTN increases dementia risk in men. In addition, it has been recently demonstrated that HTN is strongly associated with VD in both men and women similarly (Kimm *et al*., 2011). HTN has also been shown to be associated with AD, especially in men younger than 65 years. However, the association of HTN with AD is not observed in men or women over 65 years.

CONCLUSION

With aging of the population, the prevalence of dementia including AD is expected to reach an epidemic size worldwide. However, currently no cure is available for this devastating disease, and because currently approved medications are just symptomatic, they do not modify the underlying disease pathology. Although lots of preclinical studies and clinical trials for candidate medications to reduce amyloid and other targets for AD are ongoing, studies clarifying the factors related with the risk and progression of AD are needed to identify potential novel therapeutic targets. As described in this review, the prevalence/incidence of dementia and CV risk factors for dementia is quite different by sex. Because women live longer than men in most countries, the adverse impact of the risk factors may affect women in particular. In that context, drugs may have efficacy in only one sex or have different efficacy between men and women. Actually, both male and female patients were included in many studies, but most studies did not consider the issue of sex separately. Therefore, future clinical trials for new AD therapeutics should consider a deliberate stratification by sex, and an adequate sample size is needed to test the therapeutic efficacy in men and women separately. In addition, further studies are needed to understand sex-specific effects of the CV risk factors on dementia incidence and to examine the mechanisms underlying the sex differences. The resultant information may help to establish a new strategy for the development of individualized therapeutics and preventive medications for dementia.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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