Cognitive Decline in Women: The ZARADEMP Study

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Patricia Gracia-García, Elena Lobo, Javier Santabárbara, Concepción de la Cámara, and Raúl López-Antón

P. Gracia-García (✉)
Psychiatry Service, Hospital Universitario Miguel Servet, Zaragoza, Spain

Medicine Department, University of Zaragoza, Zaragoza, Spain

Instituto de Investigación Sanitaria de Aragón (ISS Aragón), Zaragoza, Spain

Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Ministry of Science and Innovation, Madrid, Spain
e-mail: pgraciag@salud.aragon.es

E. Lobo · J. Santabárbara
Instituto de Investigación Sanitaria de Aragón (ISS Aragón), Zaragoza, Spain

Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Ministry of Science and Innovation, Madrid, Spain

Preventive Medicine and Public Health Department, University of Zaragoza, Zaragoza, Spain
e-mail: elobo@unizar.es; jsantabarbara@unizar.es

C. de la Cámara
Medicine Department, University of Zaragoza, Zaragoza, Spain

Instituto de Investigación Sanitaria de Aragón (ISS Aragón), Zaragoza, Spain

Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Ministry of Science and Innovation, Madrid, Spain

Psychiatry Service, Hospital Universitario Lozano Blesa, Zaragoza, Spain

R. López-Antón
Instituto de Investigación Sanitaria de Aragón (ISS Aragón), Zaragoza, Spain

Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Ministry of Science and Innovation, Madrid, Spain

Psychology and Sociology Department, University of Zaragoza, Zaragoza, Spain
e-mail: rlanton@unizar.es

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28.1 Introduction

The aging of the world's population is well documented. According to the United Nations (UN) [1], the number of people aged 60 or over worldwide is expected to more than double from 962 million in 2017 to 2.1 billion in 2050. Moreover, given the higher life expectancy worldwide, the number of people aged 80 or over is expected to triple by 2050, from 137 million in 2017 to 425 million in 2050. In Europe, 25% of the population is already aged 60 years or over, and this figure is expected to reach 35% by 2050 [1].

The risk of cognitive impairment and dementia increases with age [2], given that advanced age is the strongest risk factor for dementia in all regions [3]. In addition, subjects with cognitive impairment have a higher risk of progression to dementia [2].

Dementia is traditionally defined as a syndrome of global deterioration of intellectual function occurring in clear consciousness and caused by brain disease; to qualify for the diagnosis, the deterioration must be severe enough to adversely affect activities of daily living (ADL) [4]. Alzheimer's disease (AD) is the most common type of dementia, accounting for an estimated 60–80% of cases [5]. Vascular dementia (VaD), defined as dementia resulting from ischemic or hemorrhagic brain lesions, is also relatively prevalent in population studies [6], being the sole cause of dementia in about 10% of dementia cases [5].

The construct "mild cognitive impairment" (MCI) has been widely used worldwide to define the gray area between intact cognitive functioning and clinical dementia [7]. MCI represents a heterogeneous entity and it is a concept in evolution

Table 28.1 Diagnostic criteria for mild cognitive impairment (MCI)

Petersen mild cognitive impairment criteria (MCI-P)	DSM-5 mild neurocognitive disorder criteria (MCI-DSM-5)
Subjective memory complaint, usually corroborated by an informant	Concern of the individual, a knowledgeable informant, or the clinician that there has been a decline in one (or more) cognitive domain
Isolated memory impairment on neuropsychological testing compared to healthy subjects matched by age and education level	A modest impairment in cognitive performance, documented by standardized cognitive assessment
Preserved general cognitive function	Cognitive decline involves memory and/or other cognitive functions (attention, language, executive function, perceptual-motor, social cognition)
Intact activities of daily living	Cognitive deficits do not affect independence in activities of daily living, but greater effort or compensatory strategies might be required
No dementia	Cognitive deficits do not occur exclusively in the context of delirium
	Cognitive deficits are not better explained by another mental disorder (such as psychosis or depression)

[7]. The first definition (by Petersen, MCI-P) [8] focused on memory problems (Table 28.1), but, thereafter, diagnostic criteria were broadened to include impairment in other areas of cognitive functioning. MCI can be classified into two subtypes: amnestic MCI (aMCI), if performance on episodic memory tests is poor, and non-amnestic MCI (naMCI), in the case of poor performance on tests covering cognitive domains other than memory, such as executive functions, language, or visuospatial abilities. The latest version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [4] recognizes mild neurocognitive disorder as a predementia stage of cognitive impairment that shares many of the features of MCI (MCI-DSM-5) (Table 28.1).

In 2015, the number of people living with dementia worldwide was 46.8 million, and this figure is predicted to increase to 131.5 million by 2050 [3]. Apart from the personal and family burden of the disease, the global cost of dementia is estimated to be US $818 billion, including medical costs, social care workforce costs, and the significant contribution from informal caregivers [3].

In 2014, 62% of people over 80 were women [9]. This survival bias and, eventually, other sex and gender differences between women and men might explain the higher prevalence of dementia reported among women [9], specifically AD [10]. However, less than half of the up-to-date scientific literature on dementia focuses specifically on women or, more generally, gender issues [9], even though a need to prioritize dementia as a global women's health issue has been recognized [9].

In this chapter, we first describe the profile of cognitive aging in women and summarize epidemiological data on cognitive impairment and dementia, specifically in women. We will then discuss biological, societal, and cultural potential risk factors for cognitive impairment and dementia in women.

28.2 Cognitive Performance in Healthy Older Women

Differences in cognitive performance between men and women are consistently discussed in the literature, despite the controversial influence of biological and sociocultural factors. Adult women show an advantage over men in tasks related to memory, verbal fluency, and fine motor skills. Conversely, they perform worse in visuospatial tasks——such as rotation of an object or space navigation——and motor tasks, ——such as throwing an object to hit a target [11].

Even in healthy subjects older than 65, there is a clear, age-related decline in performance on executive functioning (mainly inhibition), verbal fluency, verbal memory, and cognitive speed tasks [12]. Some studies suggest that the pattern of sex differences in cognition observed in young adults declines in old age [11] and that there is a decline in the cognitive functions in which women outperform men, clearly significant in verbal fluency [13]. However, other studies [14] report that such differences persist throughout the life span: older women have higher scores than men on psychomotor speed, verbal learning, and memory tests, whereas they underperform on visuo-construction and visual perception tasks [14].

28.3 Epidemiology of Cognitive Impairment and Dementia in Older Women

To document prevalence and incidence of cognitive impairment and dementia in women, we will mainly summarize findings of collaborative studies across Europe——the European Studies of Dementia (EURODEM) project——[6, 15] and worldwide, ——the Cohort Studies of Memory in an International Consortium (COSMIC) project [16]. Both include longitudinal population-based studies of cognitive aging with large samples of subjects aged 60 or over who were not identified as having dementia, such as the Zaragoza Dementia and Depression (ZARADEMP) project [17, 18], a five-wave epidemiological enquiry in which a sample of 4803 subjects living in a large Spanish city was interviewed at baseline.

28.3.1 Mild Cognitive Impairment in Women

28.3.1.1 Prevalence and Incidence of MCI

Heterogeneity in the concept and diagnostic criteria of MCI may partly explain the wide differences in its prevalence reported to date [19, 20].

When MCI was diagnosed according to the scores in the Mini-Mental State Examination (MMSE) (MCI-MMSE), defined by a score range from 24 to 27 (with a maximum of 30) [21], the collaborative COSMIC study found an overall prevalence of 12% (95% CI 11.5–12.4) and no sex differences [21]. Prevalence of MCI-MMSE increased with age, but the pattern across age groups was different for men and women: for women, the increase in prevalence was from ages 70–79 to 80–89 and for men, from ages 60–69 to 70–79 [21].

When MCI was diagnosed by a neuropsychological test representing each of the four cognitive domains (memory, language, processing speed, and executive functioning), the COSMIC study found that the strongest association with sex was for memory, with women performing better than men across the COSMIC cohorts. However, this result comes from developed nations, where women have been afforded the same educational opportunities as men [22]. Women tended to perform worse than men on all other cognitive measures but not statistically significantly so for any measure. Processing speed exhibited the strongest decline with age in both sexes. Decline in other cognitive domains showed an interaction of sex with age, with a trend toward a faster decline in women [22].

Regarding MCI subtypes, the COSMIC study [21] found an overall prevalence of 2.0% (95% CI 1.7–2.2) for aMCI and 3.9% (95% CI 3.6–4.2) for naMCI. Prevalence of aMCI did not differ significantly across age groups or by sex; however, prevalence of naMCI across age groups showed a different pattern for women and men, similar to that defined for MCI-MMSE. A meta-analysis published in 2016 [23] that examined sex differences on incidence and prevalence of MCI subtypes found only differences in the prevalence of naMCI, with a higher prevalence among women, apparently mediated by neurological conditions (since studies that specifically

Table 28.2 Epidemiological data of cognitive impairment in the overall population and, specifically, in women, found in the ZARADEMP study

	Overall	Women
Prevalence of MCI	**% (95% CI)**	**% (95% CI)**
MCI-P	6.9 (6.5–7.3)	8.3 (7.8–8.8)
MCI-DSM-5	2.5 (2.1–2.9)	3.3 (2.8–3.8)
Prevalence ratio of MCI (over men)		**OR (95% CI)**
MCI-P		0.88 (0.7–1.2)
MCI-DSM-5		1.4 (0.9–2.1)
Prevalence of global dementia	**% (95% CI)**	**% (95% CI)**
1988–1989	5.5 (2.9–9.8)	4.8
1994–1996	3.9 (3.3–4.5)	5.0
Prevalence ratio of dementia (over men)		**OR (95% CI)**
1994–1996		2.1 (1.5–3.1)
Incidence of dementia	**IR (95% CI)**	**IR (95% CI)**
Global dementia	8.6 (7.2–10.2)	9.6 (7.7–11.8)
AD	5.4 (4.3–6.7)	6.8 (5.2–8.7)
Incidence rates of dementia (over men)		**IRR (95% CI)**
Global dementia		1.3 (0.9–1.9)
AD		1.8 (1.1–3.0)

MCI mild cognitive impairment, *MCI-P* MCI according Petersen criteria, *MCI-DSM-5* MCI according DSM-5 criteria ("mild neurocognitive disorder"), *AD* Alzheimer's disease, *OR* odds ratio, *IR* incidence rate (per 1000 person-years), *IRR* incidence rate ratio, *CI* confidence interval

excluded participants with known neurological conditions did not report significant sex differences).

In the ZARADEMP study, prevalence of MCI in women varies, depending on the diagnostic criteria applied (Table 28.1), between 3.3% (MCI-DSM-5) and 8.3% (MCI-P), which is higher than the prevalence in the overall population (Table 28.2) [20]. However, in multivariate models——after controlling by age, educational level, anxiety, and depression——differences in the prevalence of MCI in women over men were not statistically significant (Table 28.2).

28.3.1.2 Outcomes of MCI in Women

MCI is consistently associated with a higher risk of progression to dementia. According to the data of a meta-analysis including seven community studies from Japan, China, Sweden, France, and Austria [24], the annual conversion rate (ACR) from MCI to AD ranged from 5.4 to 11.5% (median: 7.1%). In the ZARADEMP study [25], ACR for dementia was 1.9% for MCI-P and 3.4% for MCI-DSM-5, being 1.2 and 2.2% for AD, respectively. Subjects diagnosed with MCI had a higher risk of progression to dementia than non-cases at 4.5-year follow-up (HR = 2.9 (CI 95% 1.8–4.5) for MCI-P and HR = 5.3 (CI 95% 3.3–8.6) for MCI-DSM-5), independently of age, sex, educational level, and comorbidity with anxiety or depression [25]. In a similar follow-up period, a French community study [26] found a higher conversion rate from MCI to dementia for men (8%) than for women (6%). Moreover, they found gender-specific risk profiles. The factors significantly

associated with progression to dementia on MCI females were disability on instrumental ADL (IADL) (OR = 3.5 (95% CI 2.1–5.9)), lower education (OR = 2.2 (95% CI 1.3–3.6)), ApoE4 allele (OR = 2.1 (95% CI 1.4–4.0)), subclinical depression (OR = 2.0 (95% CI 1.1–3.6)), anticholinergic medications (OR = 1.8 (95% CI 1.0–3.0)), and age (OR = 1.1 (95% CI 1.1–1.2)) [26]. The factors significantly associated with progression to dementia on MCI males were ApoE4 allele (OR = 3.2 (95% CI 1.7–5.7)), stroke (OR = 2.8 (95% CI 1.2–6.9)), lower educational level (OR = 2.3 (95% CI 1.3–4.1)), disability on IADL (OR = 2.2 (95% CI 1.1–1.2)), and age (OR=1.2 (95% CI 1.1–1.2)) [26].

In line with previous studies [27, 28], the ZARADEMP study found an increased mortality rate for subjects diagnosed with MCI [29]. MCI-DSM-5 was associated with a significant increased risk of mortality even after controlling by age, sex, education, medical risk factors, and psychiatric conditions (OR = 1.24 (CI 95% 1.01–1.53)) [29]. Some studies stratifying their results by sex found neither significant differences by sex strata [27] nor an increased risk of mortality in MCI males compared to women [30].

28.3.2 Dementia in Women

28.3.2.1 Prevalence and Incidence of Dementia in Women

The EURODEM collaborative study, including 11 European cohorts from the community and a total of 2346 cases of dementia [15], found an age-standardized prevalence of dementia of 6.4% (4.4% for AD and 1.6% for VaD). In the United States (USA), a higher prevalence of AD (10%) is reported [5]. Prevalence of dementia increases steeply with age, with rates doubling approximately every 5 years [31]. Consistent with international literature [5, 31, 32], the EURODEMP study found that the prevalence of AD increased continuously with age and was higher in women than in men (Fig. 28.1) [15]. For VaD, an age-dependent difference in the prevalence between men and women was reported: under 85 years old, prevalence was higher in men; from that age onward, prevalence was higher in women (Fig. 28.1) [15]. Table 28.2 shows the prevalence of dementia in the ZARADEMP study [17].

Regarding the incidence of dementia, results of the EURODEMP and ZARADEMP studies are also consistent with other international reports that found an increased risk of dementia by age and in women, specifically for AD [5, 31, 32]. The EURODEMP study, recruiting 8 community cohorts, with pooled data including 836 cases of dementia and a 42,996 person-years follow-up [6, 33], found that women had a 30% higher risk of dementia. In all studies, there was an exponential increase in dementia incidence with age, even in the very old. The rates continued to increase with age in women, whereas they plateaued in men at age 85. For AD, the pooled data showed that incidence rates among women were higher and increased more steeply by age than in men, whose rates plateaued at age 85. For VaD, the incidence rates increased with age, without any substantial difference by sex. Incidence rates of dementia and AD in the ZARADEMP study are shown in Table 28.2 [18].

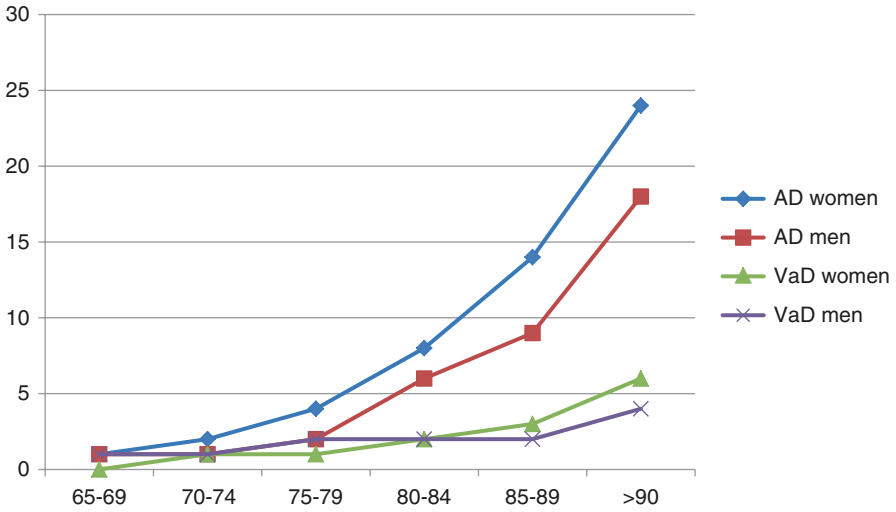

Fig. 28.1 Prevalence of Alzheimer's disease (AD) and vascular dementia (VaD) by age and sex (EURODEMP project). *Adapted, with permission from the publisher, from Lobo et al. 2000 [15]. The pooled prevalences for the groups aged 65–69, 70–74, 80–84, 85–90, and 90 and older were for AD, 0.7%, 2.3%, 4.3%, 8.4%, 14.2%, and 23.6% in women and 0.6%, 1.5%, 1.8%, 6.3%, 8.8%, and 17.6% in men, and for VaD, 0.1%, 0.6%, 0.9%, 2.3%, 3.5%, and 5.8% in women and 0.5%, 0.8%, 1.9%, 2.4%, and 3.6% in men

Public health planners use incidence rates of dementia to estimate the projected disease burden in a population. While incidence rates reflect the actual experience of a cohort, risk estimates are required to predict how much disease a population may expect. Lifetime risk (LTR), calculated at several ages, has been defined as the probability that a person of a specific age has of suffering the condition at that time in his or her life. Consistent with the results from the Framingham study in the United States [34], LTR in the ZARADEMP study [18] was reported to be higher in women than in men, both for overall dementia and AD. Lifetime probability of suffering dementia for women aged 65 was 19.7% (vs. 14.1% in men) and aged 85, 20.4% (vs. 16.8% in men). The corresponding figures for AD in women were 16.7% and 17.6% (vs. 8.4% and 10.9% in men). Differences regarding sex were independent of the educational level, although they tended to decrease in subjects older than 85 [18].

A recent review of international data investigating the changes in prevalence and incidence of dementia over time suggests a current decline in both [35]. The ZARADEMP study [17], which compares data from 1994 and 1987 (Table 28.2), and a Swedish study [36], which compares data from 2001 and 1995, did not find a significant reduction in the prevalence of dementia in the total population, but they found decreases in prevalence higher than 50% in men. Studies that investigated trends in the incidence of dementia found notable differences in subpopulations, particularly between sexes [35]. A British study, which compares data from 2008 to 1991 [37], found that a decrease in the incidence of dementia was confined to men.

The Framingham study (USA), which compares data from 2005 to 1985 [38], found that in women, the decrease occurred earlier than in men and continued over time. A French study, comparing data from 1999 to 1988 [39], found that the decrease in the incidence of dementia was driven by an effect in women. The authors [35] concluded that diagnosis of dementia, as of any disorder, is contextual and can change across time and geographies. They also reported that societal changes and improvements in living conditions, education and healthcare, as we will discuss later, might have been responsible for these observed trends.

28.3.2.2 Outcomes of Dementia in Women

Women with AD seem to deteriorate faster in the earlier stages of the disease and show poorer cognitive profiles at the same stage of dementia than men [40].

Women have a broader spectrum of dementia-related behavioral symptoms with a tendency for depression [32, 41], anxiety, and delusions [42], while aggression is more frequent in men [32].

AD is a leading cause of disability and poor health and is officially listed as the fifth leading cause of death for people aged 65 and over, despite it being frequently unrecognized as cause of death by official sources [5]. The ZARADEMP study found an increased risk of mortality in moderate and severe cases of dementia [43], and that risk increased in parallel with the degree of cognitive impairment (measured by the MMSE), with HR = 2.08 (95% CI 1.42–3.04) in the most severe stage (MMSE score <10) [44]. In this sample, severe cognitively impaired people were more likely to be women, illiterate, and widowed. However, the increased risk of mortality for cognitive impairment was independent of these and other variables related to health status, the population attributable fraction (PAF) of cognitive impairment being 3.49% (95% CI 1.38–6.40) [44]. However, a European study [45] found a higher risk of death in men with dementia than in women. Survival in subjects older than 85 at 2 years was 81% in women without dementia (vs. 76% in men without dementia) and 60% in women with dementia (vs. 52% in men with dementia). Survival at 5 years was 52% in women without dementia (vs. 44% in men without dementia) and 27% in women with dementia (vs. 16% in men with dementia) [45].

The aforementioned European study [45] found that the probability of being in institutional care increased with age and was significantly higher for cases of dementia in both sexes; however, women were more likely to be in an institution than men. This could be due to societal and cultural factors, because women take on a role as caregivers more frequently than men do [9]. Care for patients with dementia takes place 80% of the time by families and is provided by women 78% of the time [32].

28.4 Risk Factors for Cognitive Impairment in Women

In addition to several biological explanations for the sex differences observed in the prevalence and incidence of MCI and dementia, the effects of sociocultural aspects, i.e., gender differences, should also be studied [33] (Table 28.3).

Table 28.3 Potential modifiable risk factors for cognitive impairment and/or dementia in women

Risk factors for cognitive impairment in women
Estrogen depletion in early menopause (?)
Depression
Diabetes
Mid-life hypertension
Mid-life obesity
Dyslipidemia
Smoking
Alcohol (?)
Diet high in saturated fats
Low educational level
Jobs with low intellectual demand
Lack of physical exercise

(?) Factors with controversial effects

28.4.1 Biological Risk Factors

Differences on brain reserve: Women have a smaller cerebral brain volume than men [11, 46], so they have less ability to cope with pathological insults compared to men and more probability of showing clinical symptoms of AD at the same level of brain pathology [46].

Genetics: The E4 allele of the apolipoprotein E (ApoE4) is the strongest known genetic risk factor for late-onset AD; its effects have been reported to be more pronounced in women than in men [46].

Hormones: Estrogen receptors have been found in several areas related to cognition in the brain, which could explain (at least partially) differences in cognition found between women and men in adult life and the decline in some cognitive functions in women after menopause [13]. Moreover, estradiol exerts neuroprotective actions——enhancing neuronal growth and formation of synapses——and increases the synthesis of acetylcholine, which is a key neurotransmitter in the regulation of attention and memory. Therefore, depletion of estradiol could increase the risk of cognitive impairment and AD in women [13].

There is evidence in the literature of an association between a prolonged exposure to female hormones——i.e., women with later menopause and longer reproductive period——and better cognitive performance and delayed cognitive decline, despite no evidence of association between prolonged exposure to female hormones and a lower risk of dementia [47].

Hormonal therapy (HT) could have positive effects on cognition during a critical period in early postmenopause, for example, in women after a hysterectomy; however, HT positive or negative effects affect physical health for periods longer than 10 years [13].

Estrogens are also involved in the regulation of behavioral mood through interaction with the serotoninergic systems, so periods of hormonal fluctuations (such as perimenopause) are related to increased vulnerability to mood disorders such as depression [13], which is also associated with cognitive impairment and dementia in different ways.

Depression: Epidemiological studies based on community samples consistently find a higher prevalence of depression in women than in men [41]. Moreover, women are also more frequent on psychopharmacological drugs [48].

Depression has been significantly associated with MCI and dementia. In the ZARADEMP study, more than 50% of cases of depression and/or anxiety were also diagnosed with MCI-P, and more than 50% of MCI cases had comorbidity with depression or anxiety [20]. A French community study [26] also found that both women and men with MCI were more likely to have depressive symptoms and to take anticholinergic medications than cognitively healthy subjects. In said study, women with MCI were more likely to suffer from insomnia and to have poor subjective health, disability, and social isolation. The ZARADEMP study, consistently with the literature [49], found not only a frequent comorbidity between depression and dementia [41] but also a longitudinal increased risk for dementia, specifically AD, in cognitively healthy subjects with more severe depression (HR = 4.30 (95% CI 1.39–13.33)) [50].

Cardiovascular risk factors. Many factors that increase the risk of cardiovascular disease are also associated with a higher risk of dementia:

- *Diabetes:* Type 2 diabetes is a risk factor for cognitive impairment and dementia (VaD and AD) [51]. Diabetes is a relatively frequent diagnosis in the community (8.7%) [52]. Globally, more men than women are diagnosed with diabetes, but there are large sex ratio differences in the prevalence of diabetes across countries that parallel those of obesity, the most prominent risk factor for diabetes in both sexes [53]. Moreover, women have a greater relative risk of cardiovascular complications and mortality in the presence of diabetes [53].
- *Mid-life obesity* has been reported as an independent risk factor for cognitive impairment and dementia [54], specifically in women [55].
- *In some studies*, *hyperlipidemia and mid-life hypertension* have been associated with cognitive decline and dementia [54]. Hypertension, generally asymptomatic, was the most prevalent medical condition in the ZARADEMP sample (61.7%), and it was significantly more prevalent in women (65.1% (95% CI = 63.3–66.9)) [52]. Estrogens improve the lipid profile and promote vasodilatation and antioxidant activities; therefore, menopause leads to an overturn of all these effects on vascular health [13].

Survival bias: The higher overall lifetime risk of dementia in women might be influenced by the combined effect of the longer life expectancy among them and a selective survival to age 65 of men with the lowest risk of developing dementia. Mortality from cardiovascular causes starts in mid-life, so men who die earlier from cardiovascular diseases might have had, if they had survived, the highest risk of dementia [34].

28.4.2 Social and Cultural Factors

Education: Previous studies consistently found that subjects with a low educational level, specifically women, have a higher risk of AD [10, 56]. A higher level of

education has been related to an increase in cognitive reserve; therefore, subjects with a higher level of education may take longer to reach the threshold of dementia detection at a same degree of pathological insult to the brain.

Occupation: Some studies [57, 58] have reported an increased risk of cognitive impairment and/or dementia in subjects who have a predominantly manual occupation in life compared to subjects with occupations that involve higher intellectual requirement.

There are gender-specific societal changes in intellectual lifestyle across different generations and countries, in the context of specific economic, political, social, and cultural background [35]. For example, an epidemiological study recruiting a large sample of older subjects from several developed countries worldwide (SCOPE) found significant differences in the level of education by sex, more notable at university level, with a considerably greater percentage of men who had attended university (11.1%) compared to women (3.1%) [48]. In Spain, the ZARADEMP study found a significant higher proportion of illiterate women (10.1%) than men (4.2%) [59]. In the last decades, women living in developed countries are afforded the same educational and occupational opportunities as men; thus, a different sex-specific trend on incidence and prevalence of dementia might be expected in future epidemiological studies.

Lifestyle: Lifestyle behaviors may influence cardiovascular health and, also, the risk of dementia.

- **Diet:** Emerging evidence suggests that a diet low in saturated fats may be associated with reduced Alzheimer's and dementia risk [5].
- **Exercise/physical activity:** Aerobic and multimodal combined training have been reported to improve global cognition and some cognitive domains in both men and women; however, evidence in the literature suggests that physical exercise could have more positive effects on executive function in women than in men [60] and that the protective effect of physical activity on the risk of dementia could be specific to women [55].
- **Smoking**: Some studies found that smoking was associated with an increased risk of AD, specifically in men [10]. However, others reported that both men and women were affected by smoking-related neurological disturbances to a similar extent [61]. According to these studies [61], smoking is associated with dementia and deficiencies in general intellectual abilities and several cognitive domains: executive functions, cognitive flexibility, learning and memory processing speed, and working memory.
- **Alcohol:** Some studies have reported that moderate alcohol consumption may decrease the risk of dementia [55, 62–64]. However, the evidence is not strong enough, and other studies, such as the ZARADEMP study [65], did not find such a protective effect; moreover, a trend toward greater odds of dementia has been associated with heavier alcohol consumption among men and participants with an apoE4 allele [63].

In current older generations, drinking and smoking patterns have been very different between men and women, with a much higher proportion of drinkers [59, 65] and smokers [48, 59] among men. Globally, the prevalence of smoking is higher for

men than for women (40% vs. 9% in 2006); however, in the United States and Europe, the prevalence of female smoking nowadays is high (around 17% and 22%, respectively) [66] and might result in a higher risk of cardiovascular diseases and dementia in women compared to previous generations.

28.5 Conclusion

The higher prevalence of dementia among women has resulted in a growing recognition of the role of gender in dementia, with emerging evidence suggesting the need to acknowledge and prioritize dementia as a global health issue for women [9].

However, less than half of the published research focusing on dementia refers specifically to women or to gender issues [9]. In this chapter, we have discussed some differences on distribution of risk factors for cognitive impairment and/or dementia between men and women and an eventual differential vulnerability between them to such risk factors. Future research on cognitive impairment and dementia should stratify the analysis by sex for a better understanding of this issue. The understanding of sex and gender differences will help to define individualized treatment and preventive interventions for cognitive impairment.

Conflict of Interest P. Gracia-García has received honorarium and support for attendance to scientific meetings from Servier and Pfizer; C. de la Cámara has received funding to attend scientific meetings from Janssen, Lundbeck, and Otsuka. None of these companies have influenced the content of this work. The other authors declare that they have no conflict of interest.

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