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Sex differences in modifiable risk profiles for cognitive decline: findings from DeCo Chair Project

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Abstract

Dementia prevention strategies increasingly focus on modifiable risk factors, yet sex-specific risk profiles remain insufficiently characterized. In addition to biological mechanisms, social, behavioural, and environmental determinants may shape sex-specific trajectories of cognitive aging. Using the framework of the Lancet Commission on dementia prevention, intervention, and care modifiable risk factors, we investigated sex differences in cumulative risk burden and their association with cognitive decline in a community-based population.

We conducted a cross-sectional study including 1162 adults recruited in community pharmacies in Valencia (Spain) between 2018 and 2024 as part of the DeCo Chair project. A cumulative risk score based on Lancet Commission modifiable risk factors was calculated using population-attributable fraction weighting. Logistic regression analyses evaluated associations between individual risk factors and cognitive decline.

Men accumulated a higher burden of modifiable risk factors, including smoking, higher body mass index, alcohol consumption, diabetes, and hearing loss. Higher BMI and traumatic brain injury history were associated with increased odds of cognitive decline in men. In contrast, women showed higher prevalence of low cognitive reserve, physical inactivity, depression, and social isolation, which were all associated with increased likelihood of cognitive decline. Higher cognitive reserve was protective in both sexes.

These findings reveal distinct sex-specific risk profiles, with cardiometabolic and lifestyle risk factors predominating in men and psychosocial and cognitive reserve–related vulnerabilities in women. Our results highlight the importance of sex-tailored prevention strategies to optimize dementia risk reduction.

1 Introduction

Dementia is a growing global health challenge. According to the World Health Organization, more than 57 million people were living with dementia worldwide in 2021, making it a major public health priority [1]. Alzheimer's disease accounts for approximately 60–70% of dementia cases[1–3] and is characterized by the accumulation of β-amyloid plaques[4] and tau protein aggregates [5].

Despite advances in disease-modifying therapies [6], prevention remains a key strategy for reducing dementia burden [7]. The Lancet Commission on dementia prevention, intervention, and care has identified 14 modifiable risk factors that together may account for up to 45% of dementia cases. These factors include lower education, hearing loss, high low-density lipoprotein cholesterol, depression, traumatic brain injury, physical inactivity, diabetes, smoking, hypertension, obesity, excessive alcohol consumption, social isolation, air pollution, and visual impairment [8]. Understanding how these factors interact and accumulate across populations is critical for developing effective prevention strategies [7].

Emerging evidence suggests that dementia risk is not distributed equally between sexes. Women have been consistently reported to show a higher prevalence of cognitive decline and dementia than men [9–16]. However, the extent to which modifiable dementia risk factors accumulate and contribute differently to cognitive decline (CD) in men and women remains insufficiently characterized [3, 14, 17]. Identifying sex-specific risk profiles may help refine prevention strategies and improve the targeting of interventions. Previous studies have also identified female sex as a non-modifiable risk factor for CD, together with genetic susceptibility [15]. Importantly, sex differences in dementia risk cannot be explained solely by women's longer life expectancy. Increasing evidence suggests that distinct biological [10–12] and aging trajectories [11, 12, 14, 18] contribute to these disparities, including hormonal transitions across the lifespan [11, 12, 14, 19, 20], differences in brain structure [11, 14] and connectivity [11], small-vessel disease burden [11, 21], and patterns of tau accumulation [11, 12].

In this context, the present cross-sectional study aimed to examine sex differences in the distribution and impact of modifiable dementia risk factors on cognitive decline in a community-based population in Valencia (Spain). Using a cumulative risk score based on the Lancet Commission on dementia prevention, intervention, and care framework, we evaluated the burden of modifiable risk factors and their association with cognitive decline in men and women.

2 Materials and methods

2.1.- Study design

The present work is a cross-sectional study carried out in community pharmacies and associations in Valencia (Spain), in collaboration with the Muy Ilustre Colegio Oficial de Farmacéuticos de Valencia (MICOF, the Official College of Pharmacists of Valencia), which provided financial support for the project.

Different clinical and demographic data were collected contemporaneously with the screenings carried out from 2018 to 2024 through interviews. These data are part of the DeCo Chair project [22–24].

This study was reviewed and approved by the Ethical Committee for Clinical Research with Medications of the Arnau de Vilanova Health Department (CEIm 7/2022). All participants signed informed consent to participate in the study.

The study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki and its later amendments and ethical standards. All participants gave written informed consent.

2.2.- Participants selection

Individuals included in the initial population (n = 1469) were those whose informed consent was accepted and signed, and who did not have a diagnosis of AD or other dementias, mental illness, or other sensory deficits.

Of these 1469 participants, specifically for this study, those individuals ≥ 60 years (n = 1162) were included (Fig. 1).

2.3.- Assessment of cognitive status

To detect people with possible CD, three neuropsychological tests were carried out, following the recommendations of the Valencian Regional Ministry of Health [25]. Thus, participants were assessed with the following tests: Memory Impairment Screening (MIS) [26], Verbal Semantic Fluency (VSF) [27], and Pfeiffer's Short Portable Mental State Questionnaire (SPMSQ) [28]. Sensitivity, specificity, and test duration are shown in Supplementary Table 1.

Participants with at least one positive cognitive test were classified as individuals with CD, and those who did not fail any test were classified as participants without CD.

2.4.- Variables

The operationalization of the variables, including the selection of instruments, cut-off points, and scoring procedures, followed the methodology described in detail in our previous publication [29]. For this study specifically, of the 14 modifiable risk factors identified by The Lancet Commission [8], 13 were included in the present study. Air pollution was not included because all the participants live in the same urban area.

A cumulative risk SCORE was created, assigning 1 point per risk factor present (description at Supplementary Table 2).

Cognitive reserve was assessed using the Cognitive Reserve Questionnaire (CRQ), where values less than or equal to 6 indicate low cognitive reserve, values between 7 and 9 indicate medium/low cognitive reserve, values between 10 and 14 indicate medium/high cognitive reserve, and values greater than or equal to 15 indicate high cognitive reserve. Low and medium/low were assigned 1 point in the cumulative risk SCORE, while medium/high and high were scored 0 points.

Depression was assessed using the Yesavage Scale for Geriatric Depression (GDS5), in which values ≥ 2 are associated with risk of depression (1 point), and values < 2 are associated with no depression (0 points). Social isolation was evaluated utilising the Lubben Social Network Scale (LSNS6), where values of 12 or more are associated with risk of isolation (1 point). Values < 12 were assigned 0 points.

Physical inactivity was measured using the International Physical Activity Questionnaire (IPAQ). Low and moderate levels were scored as 1 point, and high intensity physical activity as 0 points. Additionally, obesity was classified according to body mass index (BMI). Normal weight scored 0 points, and obesity and overweight scored 1 point.

LDL levels ≥ 100 mg/dL were assigned 1 point, and LDL levels lower than 100 mg/dL were assigned 0 points. Alcohol consumption was defined as intake of ≥ 1 standard alcohol dose per day.

Finally, hearing loss, Traumatic Brain Injury (TBI), diabetes, hypertension, and visual loss were dichotomic variables (Yes = 1 point /No = 0 points).

2.5.- Statistical analyses

First, descriptive analyses were performed using the Chi-square test for categorical variables. For quantitative variables, the Shapiro–Wilk test was used to assess normality. Since the variables did not follow a normal distribution, Mann-Whitney U-test was applied to compare the variables between women and men.

Second, a cumulative risk SCORE separating sexes was calculated. Each variable was assigned a value of 0 or 1. Furthermore, the percentages assigned for The Lancet Commission of each factor's contribution to cognitive decline were considered [8]. Subsequently, the Mann-Whitney U-test was employed to compare the median scores between women and men. The prevalence of each risk factor was calculated, differentiating between women and men.

Finally, to assess whether the modifiable risk factors included in the study were associated with CD in women and men, logistic regression models were developed. These regressions were adjusted for age.

All statistical tests performed were two-tailed, and a p-value < 0.05 indicated statistical significance. Furthermore, it is important to note that, as this is an exploratory study which aims to uncover new working hypotheses, no multiplicity adjustments were made [30, 31]. Analyses were performed using RStudio (R version 2026.01.0 + 392) [32].

3 Results

3.1.- Study population

The final number of participants included in the study was 1162, of which 782 were women and 380 men (Fig. 1).

As shown in Table 1, there were no differences in age between women and men (p-value = 0.452). However, the percentage of men with a high level of cognitive reserve was significantly higher than that of women. In contrast, low cognitive reserve was more common among women (p-value = 0.002).

Figure 1. Flow chart of the study

Table 1
Characteristics of the participants that differentiate between women and men.

Variables	Women (n = 782)	Men (n = 380)	p-value
Age	73.0 ± 12.0	74.0 ± 12.8	0.455
Cognitive reserve			
Low	92 (11.8%)	40 (10.5%)	**0.002**
Medium/low	84 (10.7%)	40 (10.5%)	
Medium/high	131 (16.8%)	71 (18.7%)	
High	105 (13.4%)	97 (25.5%)	
Cardiovascular comorbidities			
Diabetes	150 (19.2%)	98 (25.8%)	**0.018**
Hypertension	427 (54.6%)	219 (57.6%)	0.340
LDL	110.0 ± 42.0	102.0 ± 42.0	0.126
Obesity			
BMI	26.6 ± 5.4	26.9 ± 4.2	0.104
Muscle mass	39.8 ± 5.2	54.8 ± 9.7	**< 0.001**
Body fat	36.6 ± 8.5	26.4 ± 8.7	**< 0.001**
Physical activity			
Low	125 (16.0%)	48 (12.6%)	**< 0.001**
Moderate	206 (26.3%)	116 (30.5%)	
High	79 (10.1%)	81 (21.3%)	
Depression			
GDS5			
No risk	285 (36.4%)	202 (53.2%)	**0.008**
Risk	148 (18.9%)	47 (12.4%)	
Social isolation			
LSNS6			
No risk	355 (45.4%)	211 (55.5%)	0.756

Note. Data are presented as number (proportion, %) and median (interquartile range).

Variables	Women (n = 782)	Men (n = 380)	p-value
Risk	58 (7.4%)	37 (9.7%)	
Hearing loss	155 (19.8)	114 (30.0)	**0.011**
Visual loss	64 (8.2)	31 (8.2)	0.194
Traumatic brain injury	20 (2.6)	12 (3.2)	0.884
Tobacco			
Ex - smoker	152 (19.4%)	175 (46.1%)	**< 0.001**
Smoker	50 (6.4%)	40 (10.5%)	
Passive smoker	34 (4.3%)	16 (4.2%)	
Non-smoker	545 (69.7%)	151 (39.7%)	
Cognitive variables			
SMQ	487 (62.3%)	172 (45.3%)	**< 0.001**
Cognitive decline	227 (29.0%)	98 (25.8%)	0.249
Pffeifer			
No risk	643 (82.2%)	332 (87.4%)	**0.038**
Risk	140 (17.9%)	50 (13.2%)	
MIS			
No risk	680 (87.0%)	320 (84.2%)	0.225
Risk	103 (13.2%)	60 (15.8%)	
FVS			
No risk	687 (87.9%)	342 (90.0%)	0.230
Risk	95 (12.1%)	37 (9.7%)	
Note. Data are presented as number (proportion, %) and median (interquartile range).			

Abbreviations: BMI: body mass index; GDS5: Geriatric Depression Scale – 5 items; LSNS6: Lubben Social Network Scale – 6 items; SMQ: subjective memory complaint; MIS: Memory Impairment Screen; FVS: Verbal Fluency Score. **P-value** <0.05

Regarding cardiovascular comorbidities, diabetes was more prevalent among men (p-value = 0.018). Nevertheless, muscle mass was higher and body fat lower in male participants compared to women (p-

value <0.001). In addition, men were more prone to practicing high-intensity physical activity (p-value <0.001). Smoking was also more prevalent among men compared to women (p-value <0.001).

Finally, depression (p-value = 0.008) and subjective memory complaint (SMC) (p-value <0.001) were more common in women than in men.

3.2.- Cumulative risk SCORE and prevalence of the different risk factors

As illustrated in Figure 2, the median cumulative risk SCORE in men compared to women is significantly higher (Women: 15.75 ± 11.3; Men: 17.06 ± 13.9; p-value < 0.001).

Figure 2. Violin plot of the weighted risk SCORE in women and men. Test: Mann-U Whitney

Women (median ± interquartile range): 16.9 ± 11.3

Men (median ± interquartile range): 18.3 ± 13.9

Using the scoring given for the cumulative risk SCORE calculation, the prevalence of each risk factor was calculated. Low cognitive reserve (p-value = 0.010), physical inactivity (p-value <0.001), and depression (p-value <0.001) were significantly more prevalent among women (Figure 3 and Supplementary Table 3). Nevertheless, diabetes (p-value = 0.023), high BMI (p-value = 0.002), hearing loss (p-value = 0.014), alcohol consumption (p-value <0.001), and tobacco (p-value <0.001) were more prevalent in men (Figure 3 and Supplementary Table 3).

Figure 3. Prevalence of risk factors for cognitive impairment, stratified by sex

Abbreviations: LDL: low-density lipoprotein; BMI: body mass index; TBI: traumatic brain injury. *P-value < 0.001 ***, <0.01 **, <0.05 **

3.3.- Association between the 13 modifiable risk factors and CD

Compared to having low level of cognitive reserve, medium/low (Women: [0.50 (0.26, 0.95); p-value = 0.035]; Men: [0.34 (0.13, 0.87); p-value = 0.028]), medium/high (Women: [0.27 (0.14, 0.50); p-value <0.001]; Men: [0.24 (0.09, 0.58); p-value = 0.002]) and high level of cognitive reserve (Women: [0.23 (0.11, 0.45); p-value <0.001]; Men: [0.17 (0.07, 0.41); p-value <0.001]) were associated with less CD in both, women and men (Figure 4 and Supplementary Table 4).

Figure 4. Forest plot of the comparison of the odds ratio (ORs) and confidence intervals (CI) of the different risk factors for cognitive decline in women and men.

Abbreviations: LDL, low density lipoprotein; BMI, body mass index; TBI, traumatic brain injury

Reference categories: Cognitive reserve: low level; LDL: < 100; Physical activity: low intensity; Tobacco: non-smoker; all other variables: absence of the condition

P-value < 0.001 ***, <0.01 **, <0.05 *

Additionally, high BMI (Women: [1.03 (0.99, 1.07); p-value = 0.117]; Men: [1.06 (1.00, 1.14); p-value = 0.044]) and TBI (Women: [0.82 (0.23, 2.35); p-value = 0.729]; Men: [4.46 (1.27, 15.84); p-value = 0.018]) were associated with increased likelihood of developing CD, but only in men (Figure 4 and Supplementary Table 4).

In women, social isolation [2.15 (1.17, 3.90); p-value = 0.012] and depression [1.68 (1.06, 2.67); p-value = 0.027] may increase the likelihood of CD. In contrast, high intensity physical activity compared to low intensity, may be beneficial [0.26 (0.10, 0.58); p-value = 0.002].

4 Discussion

In this cross-sectional study of 1162 participants, a cumulative risk score was calculated using 13 of the 14 modifiable risk factors for dementia established by the Lancet Commission, weighted by their respective population-attributable fractions. This score showed that men had higher values than women, suggesting that men accumulate more modifiable risk factors for CD than women.

Moreover, in our study, we have also examined the prevalence of these factors by sex. As shown in Figure 5, smoking, higher BMI values, drinking more alcohol, diabetes, and hearing loss were more prevalent among men. Additionally, logistic regression analyses showed that higher BMI and a history of TBI were associated with increased odds of CD in men. In contrast, lower cognitive reserve, engaging in less physical activity, and reporting depressive symptoms were more prevalent among women. Furthermore, these factors, along with social isolation, were associated with a higher likelihood of CD in women.

Figure 5. Overview of modifiable CD risk factors in women and men

Abbreviations: TBI: traumatic brain injury

Created in https://BioRender.com

It has been hypothesized that women experience a slower rate of CD before menopause; however, after menopause, this decline accelerates, leading to faster cognitive deterioration compared to men [12,18,20]. This finding is consistent with a longitudinal study showing that, in midlife, women performed better cognitively than men, but most sex differences in cognitive function diminished with aging [9]. Oestrogen receptors are distributed throughout the brain and regulate various physiological processes [12,20,33]. Indeed, some studies suggest that oestrogen may reduce beta-amyloid levels [12] and exert anti-inflammatory and antioxidant effects [20]. During menopause, there is a marked decrease in oestrogen levels [20], which may partly explain the observed acceleration of cognitive decline in women after menopause [14]. Nevertheless, a study involving 66670 participants found no significant sex differences in cognitive decline across the studied outcomes [34].

A further explanation for the higher prevalence of CD among women has been the lower levels of education. Education level has been identified as a significant risk factor for both dementia and CD [8]. Limited access to education reduces cognitive reserve and heightens CD vulnerability [35]. Historically, access to education has been restricted to men [11–14,18,19,35,36], while women have been confined to occupational roles that often limit their autonomy and remuneration and provide minimal cognitive stimulation [3,35]. Although low cognitive reserve is more prevalent among women in our cohort, higher levels of cognitive reserve have been shown to consistently lower CD likelihood across both sexes. Recent longitudinal analyses have revealed dynamic sex differences in late-life cognition. Women from later birth cohorts have been shown to exhibit better memory, attenuated fluency deficits, and slower memory decline. This highlights the role of education in narrowing the historical cognitive gaps between the sexes [36].

Furthermore, previous research has reported that women tend to have more adverse psychosocial profiles [18,20,37,38], whereas men more often exhibit unfavourable cardiovascular profiles [37]. However, after menopause, cardiovascular diseases increasingly affect women, being the leading cause of death among women worldwide [20]. Oestrogens also play an important role in cardiovascular health [20], which may partly account for these sex-specific patterns in cardiovascular risk. This agrees with our outcomes, diabetes and higher BMI were more prevalent among men. On the contrary, depression increased the likelihood of CD by almost 70%, and social isolation doubled this likelihood in women.

Additionally, our results show that engaging in physical activity decreases the likelihood of CD by almost 75% in women. This is consistent with previous research in which physical inactivity has been associated with an increased risk of dementia [13,20]. Physical activity has been socially framed as a predominantly male activity, which may have limited women’s participation [14,39]. Nonetheless, prior evidence suggests that women may derive greater benefits from physical activity in later life, particularly in domains such as cognitive function, emotional well-being, and neural structure [35].

Men, in contrast, are more likely to participate in high-intensity activities and a broad range of sports that entail a higher risk of head impacts and injuries [18]. These are major sources of TBI. This pattern of exposure is relevant because TBI is a potentially modifiable risk for AD and other dementias [8]. Indeed, existing studies indicate an association between participation in professional contact sports and an increased risk of neurological disorders and neurodegenerative diseases [40]. These findings align with our results, which show that men who have experienced TBI face four times higher odds of CD than those who have not experienced it.

Finally, consistent with prior epidemiological evidence [19,20,35,41], our results confirm that men exhibit a higher prevalence of smoking and excessive alcohol consumption, two modifiable risk factors independently linked to increased dementia risk [8]. These behavioural patterns likely contribute to men's elevated cumulative risk scores observed in our cohort.

These findings suggest that women’s excess risk may not be explained solely by historically lower educational opportunities, as cognitive reserve appears to have a similar impact on women and men.

Rather, they support the idea that women and men differ in their physiological vulnerability and in their risk profiles. This highlights the need for personalised prevention strategies and for further studies that explicitly incorporate sex differences in the assessment and modelling of dementia risk.

Strengths and limitations

One of the main strengths of this study is the use of face-to-face interviews, with all participants assessed in person during approximately one-hour structured interviews. This direct approach allowed for a comprehensive and standardized collection of clinical, lifestyle, and psychosocial data, reducing the risk of misinterpretation, missing information, and reporting bias commonly associated with self-administered or online questionnaires. Moreover, in-person assessments facilitated clarification of responses, improved data accuracy, and ensured inclusion of participants who might otherwise be underrepresented in digital-based studies, thereby enhancing the overall quality and reliability of the dataset.

However, this study, while providing relevant evidence on the relationship between CD risk factors and sex in older adults, has several limitations that should be considered.

First, the cross-sectional design limits the ability to infer causality between sex, risk factor burden, and CD. Although significant associations were observed, it is not possible to draw definitive conclusions about causality. The cross-sectional nature of the data does not allow examination of how risk factors and cognition change over time or how their trajectories may differ between women and men.

In addition, the sample was recruited from community pharmacies and associations in the Valencian Community, using the same database as our previous work. This recruitment strategy and geographical restrictions may limit the generalizability of the findings to other regions or populations.

These limitations highlight the need for larger, longitudinal studies that address these questions and allow for a more complete understanding of sex-specific patterns in dementia risk factors and cognitive outcomes. Despite these limitations, the findings of the present study contribute significantly to knowledge about sex differences in CD risk profiles in older adults and may help inform tailored prevention strategies.

5 Conclusion

Our findings reveal distinct sex-specific profiles of modifiable risk factors associated with cognitive decline. Men showed a higher burden of cardiometabolic and lifestyle-related risk factors, whereas women presented greater prevalence of psychosocial vulnerabilities and lower cognitive reserve. Importantly, higher cognitive reserve was associated with a reduced likelihood of cognitive decline in both sexes.

These results suggest that differences in modifiable risk profiles may contribute to sex disparities in cognitive aging. Considering sex-specific patterns of risk accumulation may therefore help refine

dementia prevention strategies and support the development of more targeted and effective interventions.

Integrating sex as a biological and social variable in dementia risk assessment could improve the design of preventive strategies aimed at reducing the global burden of cognitive decline.

Declarations

Author contributions

Conceptualization: MGZ, MGP and LM; **Data curation**: MGZ and JP; **Formal analysis**: MGZ and JP; **Funding acquisition**: LM; **Investigation**: MGZ; **Methodology**: MGZ; **Project administration**: JP and LM; **Resources**: MGZ; **Software**: MGZ; **Supervision**: JP and LM; **Validation**: MGP, JP and LM; **Visualization**: MGZ, MGP, JP and LM; **Writing-original draft**: MGZ; **Writing-review and editing**: MGP, JP and LM.

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Data availability

Data will be available upon request

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the author(s) used chat GPT in order to rectify grammatical errors and enhance the clarity of the language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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Figures

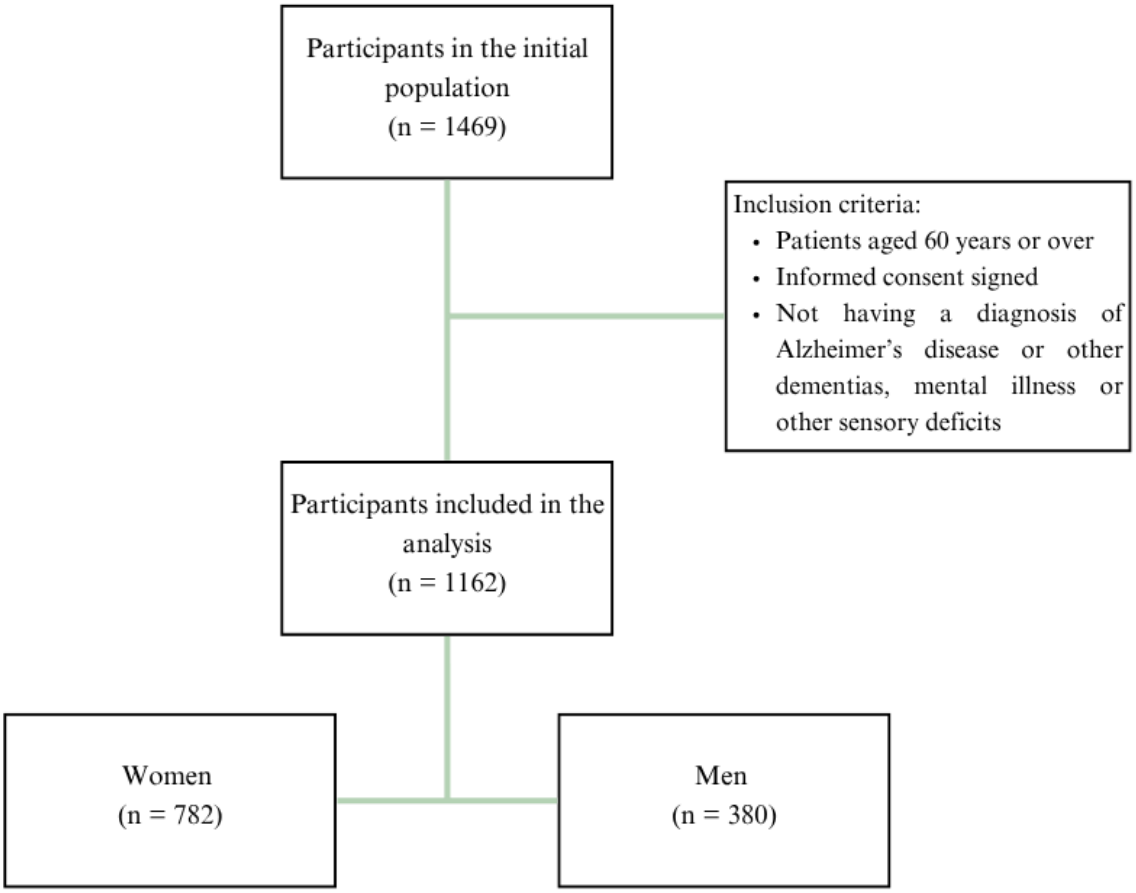


Figure 1

Flow chart of the study

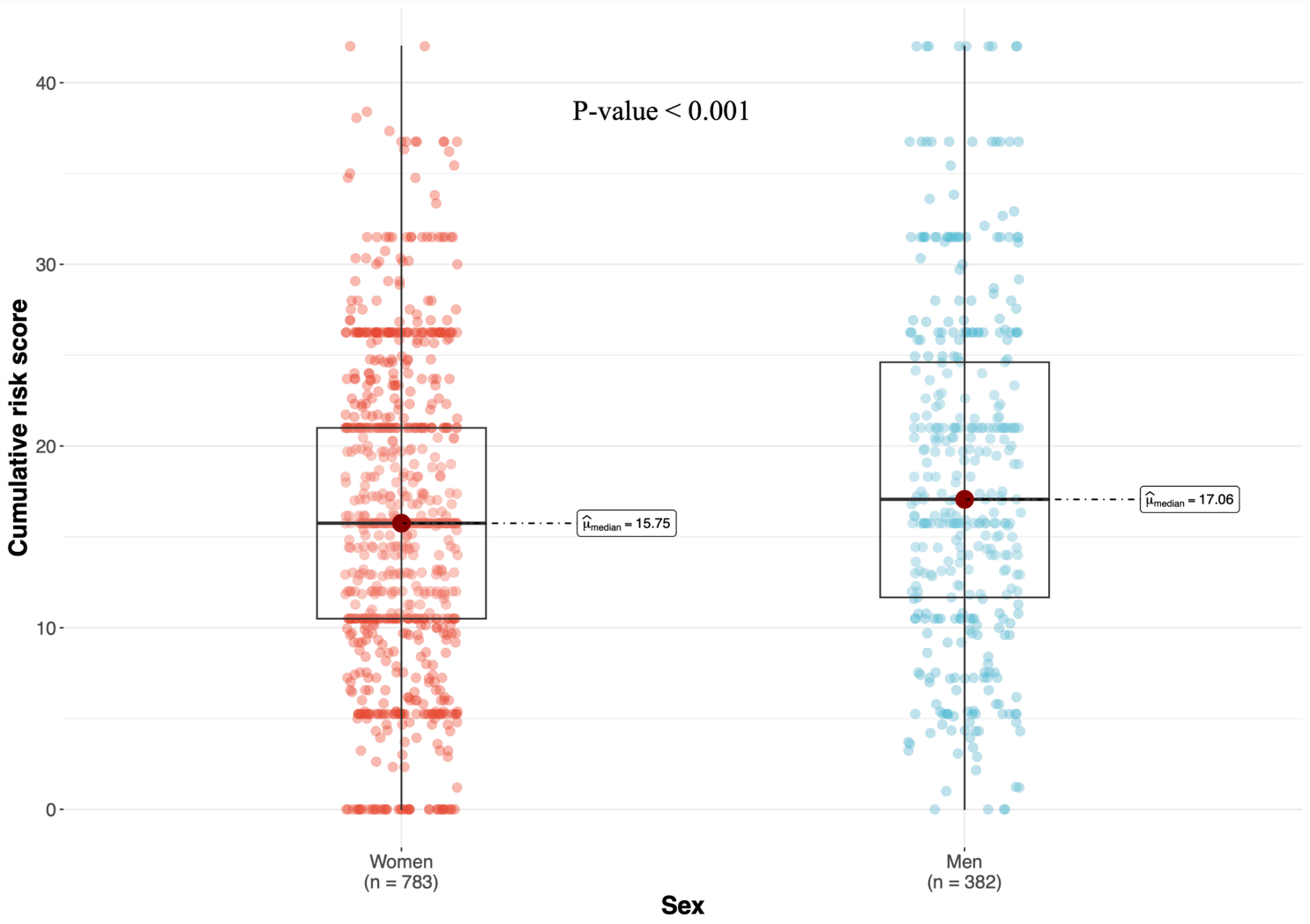


Figure 2

Violin plot of the weighted risk SCORE in women and men. Test: Mann-U Whitney

Women (median ± interquartile range): 16.9 ± 11.3

Men (median ± interquartile range): 18.3 ± 13.9

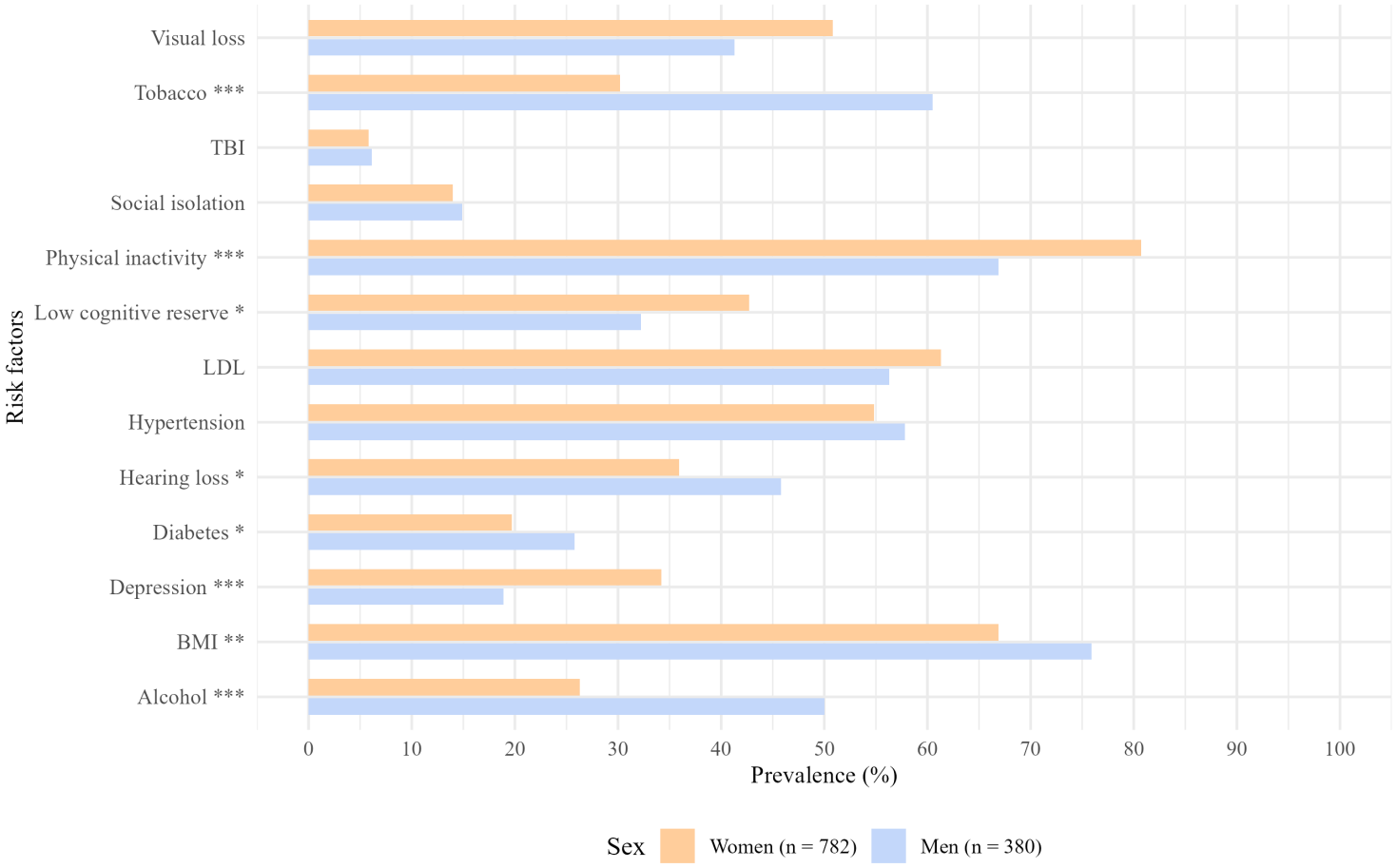


Figure 3

Prevalence of risk factors for cognitive impairment, stratified by sex

Abbreviations: LDL: low-density lipoprotein; BMI: body mass index; TBI: traumatic brain injury. *P-value < 0.001 ***, <0.01 **, <0.05 **

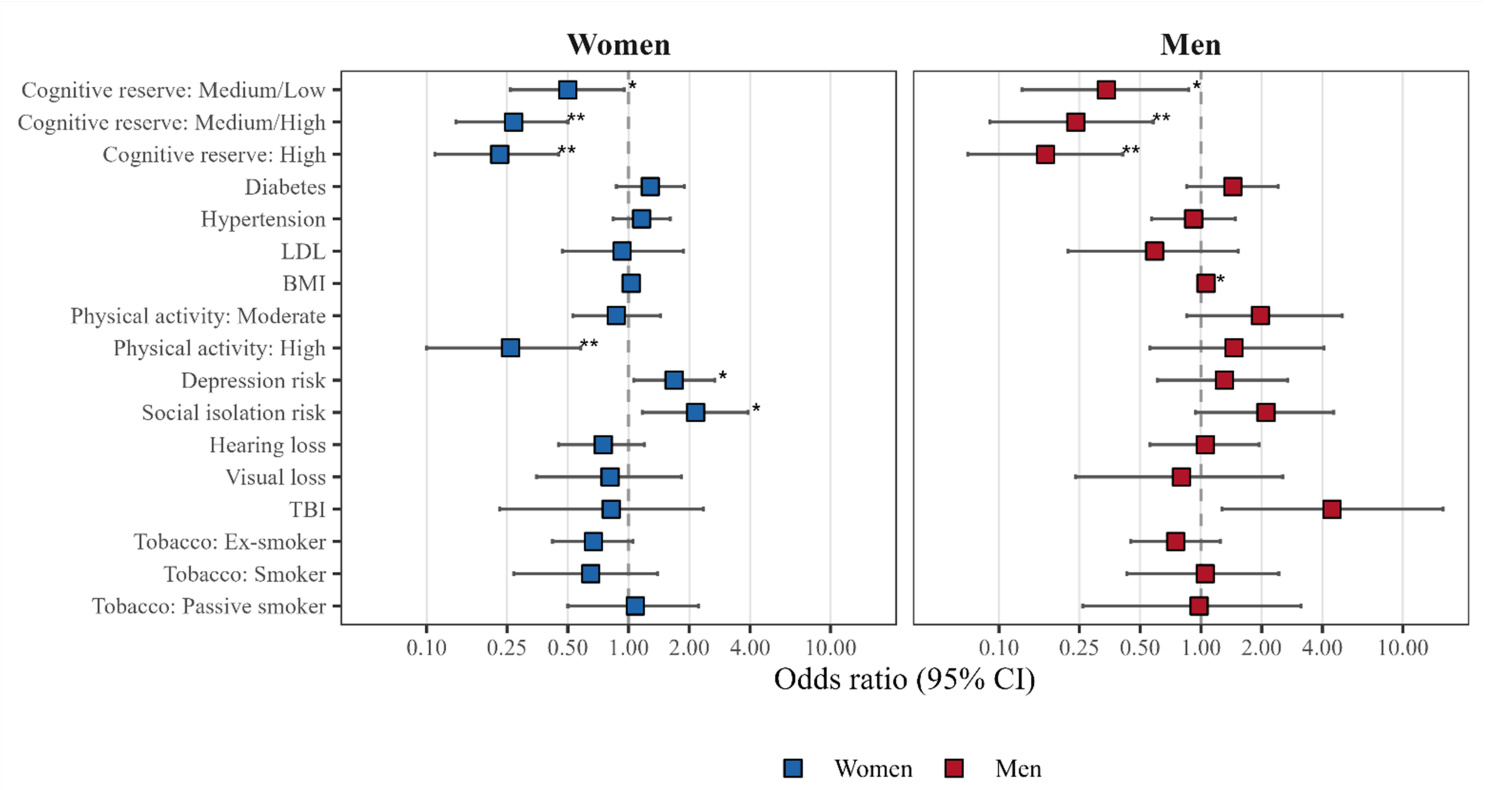


Figure 4

Forest plot of the comparison of the odds ratio (ORs) and confidence intervals (CI) of the different risk factors for cognitive decline in women and men.

Abbreviations: LDL, low density lipoprotein; BMI, body mass index; TBI, traumatic brain injury

Reference categories: Cognitive reserve: low level; LDL: < 100; Physical activity: low intensity; Tobacco: non-smoker; all other variables: absence of the condition

P-value < 0.001 ***, <0.01 **, <0.05 *

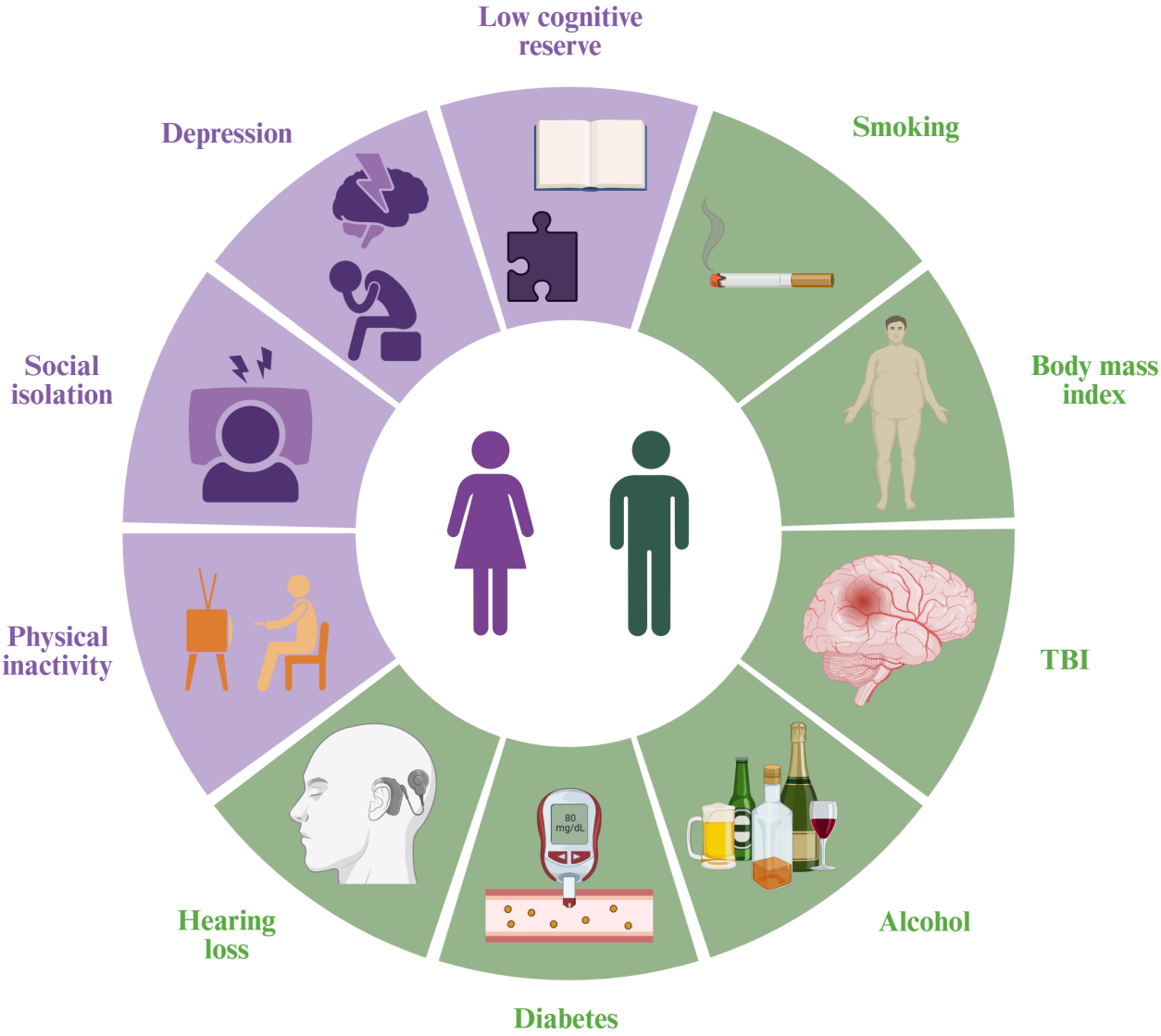


Figure 5

Overview of modifiable CD risk factors in women and men

Abbreviations: TBI: traumatic brain injury

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Supplementary Files

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