Received: 20 February 2026 | Revised: 4 May 2026 | Accepted: 5 May 2026

DOI: 10.1002/dad2.70379

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Polypharmacy is associated with lower progression from MCI to Alzheimer's disease, with sex-specific patterns across drug classes

Mar García-Zamora[1,2] | Juan Pardo[3] | Miriam Esteve[4] | Alejandro Martinez-Gracia[4] | Consuelo Cháfer-Pericás[1] | Antonio Falcó[4]

[1]Research Group in Alzheimer Disease, Instituto de Investigación Sanitaria La Fe, Valencia, Spain

[2]Department of Pharmacy, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia, Spain

[3]Department of Mathematics, Physics and Technological Sciences, Universidad Cardenal Herrera-CEU, CEU Universities, Valencia, Spain

[4]Department of Mathematics, Physics and Technological Sciences, Universidad Cardenal Herrera-CEU, CEU Universities, Elche, Spain

Correspondence
Juan Pardo, Universidad Cardenal Herrera-CEU, CEU Universities, E46115 Valencia, Spain.
Email: juaparal@uchceu.es

Antonio Falcó, Department of Mathematics, Physics and Technological Sciences, Universidad Cardenal Herrera-CEU, CEU Universities, Elche, Spain.
Email: afalco@uchceu.es

Funding information
Universidad CEU Cardenal Herrera, Spain, Grant/Award Numbers: INDI25/17, GIR25/14; Banco Santander, Grant/Award Number: Ayudas a la formación de jóvenes investigadores SANTANDER-CEU

Abstract

INTRODUCTION: Polypharmacy is often considered harmful in older adults, yet several cardiovascular and psychiatric drugs target modifiable dementia risk factors. We examined the association between polypharmacy and progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD), overall and by sex.

METHODS: In a retrospective cohort of 4557 adults ≥ 50 years with MCI, followed for a mean of 68.7 months, polypharmacy was defined as ≥ 5 medications. Cox models adjusted for age and sex estimated hazard ratios (HRs), including sex-stratified analyses.

RESULTS: Polypharmacy may be associated with lower likelihood of progression to AD. Sex-stratified analyses suggested differences: antidiabetics, antithrombotics, sedatives, and antidepressants were mainly associated with lower progression in women; antihypertensives in men; anxiolytics, antipsychotics, and antidementia drugs in both sexes.

DISCUSSION: These observational findings indicate possible associations between medication use and MCI to AD progression, with potential sex-specific patterns, but causality cannot be inferred. Unmeasured factors and limited covariate adjustment may contribute.

KEYWORDS
Alzheimer's disease, cardiovascular drugs, mild cognitive impairment, polypharmacy, psychiatric drugs, sex differences

Highlights

- Polypharmacy was associated with a lower likelihood of progression from mild cognitive impairment to Alzheimer's disease.

Mar García-Zamora and Juan Pardo contributed equally to this work.

Consuelo Cháfer-Pericás and Antonio Falcó have contributed equally as last authors.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2026 The Author(s). *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

- A graded protective effect was observed with increasing medication count.
- Distinct sex-specific associations emerged across cardiovascular and psychiatric drug classes.
- Antidiabetics, antithrombotics, sedatives, and antidepressants were protective mainly in women, and antihypertensives in men.

1 | INTRODUCTION

Dementia is a syndrome characterized by progressive decline across multiple cognitive domains that ultimately interferes with independence in activities of daily living.[1] Alzheimer's disease (AD) is the most common form of dementia, accounting for ≈ 60% to 80% of all dementia cases worldwide.[2–5] AD is a highly heterogeneous disorder, with substantial variation in pathology onset and progression among individuals.[5]

Mild cognitive impairment (MCI) is considered a prodromal stage of dementia and, in many cases, a precursor of AD dementia.[6] MCI is defined by cognitive decline beyond what is expected for an individual's age and education level, yet it does not significantly interfere with daily activities.[7] MCI carries a high risk of progression to AD,[6,8,9] with annual conversion rates often ranging from 8% to 15% and cumulative risk exceeding 80% over several years of follow-up.[7] Identifying factors that delay the transition from MCI to AD could result in a 57% reduction in AD prevalence.[9] Therefore, this is a major clinical and public health priority.[7]

Among the determinants that influence progression from MCI to AD dementia, age and female sex have consistently emerged as key risk factors, alongside clinical and genetic contributors.[7] However, 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.[10–15] Evidence suggests that distinct biological[13,14,16] and aging trajectories[14,16–18] contribute to these disparities, including hormonal transitions across the lifespan;[14,16,17,19,20] differences in brain structure[14,17] and connectivity;[14] small-vessel disease burden;[14,21] and patterns of tau accumulation.[14,16] Some of these factors may also influence drug metabolism and efficacy in men and women.[5]

In addition, female sex has been associated with a higher prevalence of polypharmacy and a greater likelihood of potentially inappropriate drug usage.[4,5,22,23] These observations support the evaluation of sex as a potential effect modifier in the association between polypharmacy and progression to AD. Nevertheless, few studies have stratified by sex.

Polypharmacy, defined as the use of five or more medications simultaneously, has become the norm in many older patients.[5] However, the role of polypharmacy in dementia remains controversial. Numerous studies have reported detrimental effects on cognitive impairment and dementia,[23–26] while others have found protective or null associations.[27,28]

As a marker of multimorbidity, polypharmacy may reflect the presence of multiple chronic conditions,[29] such as diabetes, hypertension, hypercholesterolemia, cardiovascular disease, and depression.[5,28] Several of these conditions are also modifiable risk factors for dementia.[10] In addition, some medications used to treat these conditions, such as cardiovascular and psychotropic medications, are among the top prescribed multidrug therapies.[5] It is important to acknowledge key pharmacoepidemiologic challenges when studying medication use in older adults, including confounding by indication, in which the underlying disease may influence both medication use and dementia risk, and reverse causation, in which early cognitive decline may lead to increased prescribing. Conversely, polypharmacy may also represent a modifiable exposure by which medication-related factors such as pharmacological properties, therapeutic appropriateness, and potential cognitive effects may be more relevant than the total number of drugs.[27]

Therefore, drug repurposing has emerged as a key strategy in AD research.[9,30,31] This approach involves evaluating approved medications for their potential to prevent, delay, or modify the course of AD pathology.[30,31] A considerable proportion of candidate therapies in the current AD drug development pipeline consists of repurposed agents, and multidrug therapies commonly used in older populations may exert protective effects by improving long-term control of comorbidities strongly linked to AD and related dementias.[5] This perspective suggests that, beyond the sheer number of medications, the clinical appropriateness, therapeutic targets, and combinations of drugs may critically shape the relationship between polypharmacy and dementia risk.

Within this context, the aim of the present study was to investigate in a large population the association between polypharmacy and progression from MCI to AD in a real-world clinical cohort, considering both the total number of concomitant medications and the role of major cardiovascular and psychiatric drug classes, while acknowledging that any observed effects may be related to underlying diseases rather than the medications themselves. A further objective was to evaluate these associations specifically within each sex. Given the known biological and clinical differences in dementia progression between women and men, we aimed to characterize the distinct impact of polypharmacy, the number of drugs, and specific medication groups on the risk of conversion from MCI to AD for each group independently.

2 | METHODS

2.1 | Study design, setting, and participants

The present work is a retrospective cohort study based on electronic health records (EHRs) provided by the *Consellería de Sanitat Universal i Salut Pública* (Valencian Regional Health Authority, Spain), covering

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature via PubMed focusing on "polypharmacy," "mild cognitive impairment," "Alzheimer's disease," "cardiovascular drugs," "psychiatric drugs," and "sex differences." While polypharmacy is typically viewed as deleterious, emerging evidence suggests potential neuroprotective effects for certain medication classes.
2. **Interpretation**: Our findings suggest that polypharmacy is associated with a reduced likelihood of progression from mild cognitive impairment to Alzheimer's disease, showing distinct sex-specific patterns. This association may reflect the benefits of comprehensive comorbidity management, though potential surveillance bias and unmeasured confounding should be considered.
3. **Future directions**: Prospective studies and clinical trials are needed to confirm these associations, elucidate underlying mechanisms, and evaluate targeted multidrug strategies stratified by sex to guide precision approaches in dementia prevention.

the period between 2002 and 2021. Data were obtained from two different hospitals in Valencia: Arnau de Villanova and Hospital La Fe.

The initial dataset was constructed from longitudinal clinical records comprising 11,069 diagnostic instances of anonymized patients. Of the 11,069 individuals, we selected 4557 participants aged ≥ 50 years who initially presented with MCI. In addition, we included only participants who had been taking medications for at least 6 months, with the start of the medication use occurring at least 6 months prior to the MCI diagnosis. Participants with a diagnosis of AD before the MCI diagnosis were excluded, as were those with other types of dementia (non-AD). Medication use initiated after the MCI diagnosis was not considered in the analyses. Furthermore, only participants who had at least 1 year between the MCI diagnosis and any subsequent AD diagnosis were included.

The index date was defined as the first recorded MCI diagnosis. A flowchart summarizing cohort selection and the study design, including the timing of medication use and outcome assessment, is presented in Figure 1.

This research was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee for biomedical research at CEU Cardenal Herrera University (CEEI23/423) and by the Ethics Committee at the Health Research Institute La Fe (CEIM22/537).

2.2 | Drug exposure

Drug exposure was coded according to the Anatomical Therapeutic Chemical (ATC) classification system. To be considered exposed, participants had to have been taking the medication for at least 6 months, with treatment initiation occurring at least 6 months prior to the index date. This ensured that all individuals had sustained exposure before the first recorded MCI diagnosis.

For instance, an individual with a first prescription in January 2010 would need to continue taking the drug for at least 6 months (until June 2010) to meet the exposure criteria. The MCI diagnosis would need to occur after January 2011, ensuring the required prediagnosis exposure period.

Medication exposure was treated as a fixed variable, defined prior to the index date, and was not updated during follow-up. Follow-up began at the index date (MCI diagnosis) and ended at the earliest of the following: discontinuation of the medication, diagnosis of AD, or end of the study period (mean follow-up: 68.7 ± 32.5 months).

2.3 | Polypharmacy, medication counts, and drug classes

Polypharmacy was defined as the concomitant use of ≥ 5 medications. In addition, medication exposure thresholds were set from 1 to ≥ 10 to see how different levels of medication use affected MCI to AD progression.

Furthermore, we analyzed cardiovascular and psychiatric medications due to their high prevalence among older adults and because conditions such as diabetes, hypertension, hyperlipidemia, and psychiatric disorders (e.g., depression) are established risk factors for dementia.[10] Other drugs listed in File S1 in supporting information were not analyzed individually because they are not typically used to treat established dementia risk factors.

2.4 | Assessment of MCI and AD

The diagnoses of MCI and AD were made using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM codes),[32] widely used in clinical data.[27,28,30,33] Specifically, ICD-10-CM code G31.84 was used to identify patients with MCI, whereas codes beginning with G30 were used for AD.

Two groups were defined: MCI without progression for individuals who did not transition to AD and MCI to AD. For the latter group, the interval between MCI and AD diagnoses had to be at least 1 year to reduce potential misclassification due to the prodromal phase of AD and to increase the reliability of the results. In clinical practice, some patients initially diagnosed with MCI may receive an AD diagnosis shortly thereafter, even within a few months. Setting a minimum 1-year interval helps ensure that the recorded progression reflects true cognitive decline rather than rapid diagnostic reclassification. While some studies use longer intervals of 4 years,[33,34] applying such criteria in our cohort would have substantially reduced the sample size.

Participants with any diagnosis of cognitive impairment or AD before the index date were excluded. Furthermore, individuals diag-

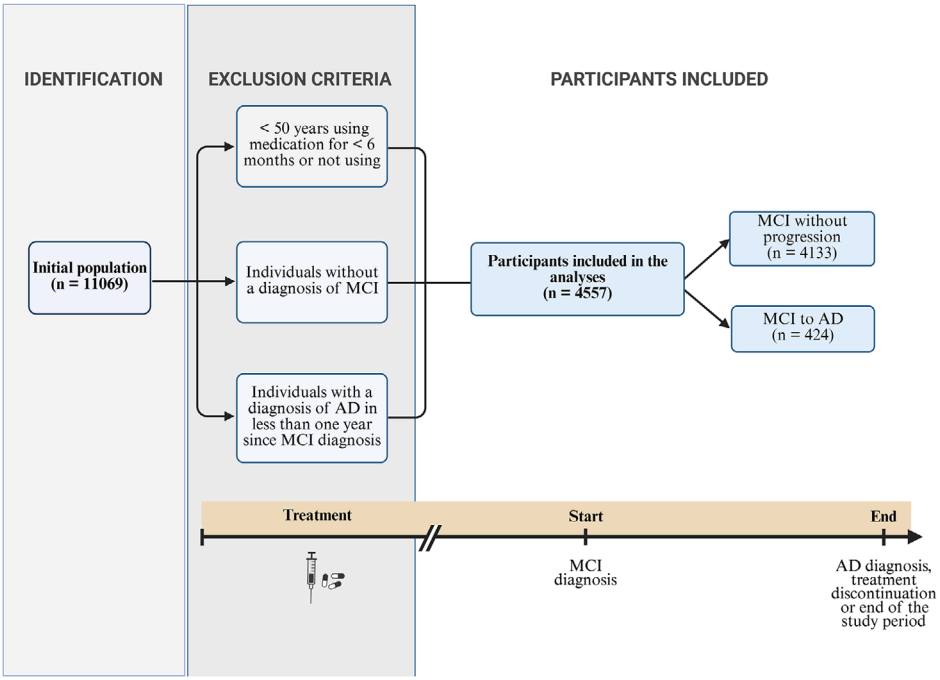


FIGURE 1 Flowchart and study design. AD, Alzheimer's disease; MCI, mild cognitive impairment.

nosed with other types of dementia (no AD), including mixed dementias, were excluded from the analyses.

2.5 | Covariates

Variables in the database were classified as demographic or clinical. Demographic variables included age, sex, and health department. Clinical variables included drug usage, assessed through prescriptions using ATC codes (list in File S1), the exposure time to the drugs in months, and clinical diagnoses ascertained using the ICD-10-CM codes.

2.6 | Statistical analysis

Descriptive analyses were conducted to compare demographic and clinical characteristics across the two study groups: MCI without evolution and those with MCI to AD evolution. Categorical variables were compared using the chi-squared test. For quantitative variables, normality was assessed using the Shapiro–Wilk test. Variables with a normal distribution were analyzed using *t* tests.

To evaluate the risk of clinical progression over time, we used time-to-event analyses, focusing on the time elapsed from the initial MCI diagnosis to AD progression.

These analyses were performed using Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between polypharmacy and the likelihood of progression from MCI to AD. The main model was adjusted for age and sex, and additional analyses stratified by sex were adjusted for age. Kaplan–Meier survival analyses were also conducted.

Cox proportional hazards models were fitted to estimate HRs and 95% CIs for the association between the total number of concomitant medications and the likelihood of progression from MCI to AD in the overall sample and stratified by sex. The number of drugs was modeled categorically, with one medication as the reference category. The overall model was adjusted for age and sex; sex-stratified models were adjusted for age only.

Cardiovascular risk medications and psychiatric medications were analyzed jointly using multivariate Cox proportional hazards models to estimate HRs and 95% CIs for the association between these drug groups and progression from MCI to AD. The overall models were adjusted for age and sex, and sex-stratified models were adjusted for age.

The proportional hazards assumption was tested using statistical methods. Schoenfeld residuals for each covariate and for the global model were calculated to identify non-proportionality. No significant violations were observed (all p values > 0.05). Additionally, p values from the Cox proportional hazards models (including polypharmacy, the number of drugs and drug classes, both in the overall population and stratified by sex) were adjusted using the false discovery rate (FDR; Benjamini–Hochberg) correction. Finally, interaction terms between sex and each exposure (polypharmacy, number of medications, and individual drug classes) were included.

All statistical tests performed were two tailed, and a p value < 0.05 indicated statistical significance. Analyses were performed in RStudio (version 2024.12.0+467).[35]

3 | RESULTS

3.1 | Demographic and clinical description of the study participants

After applying predefined inclusion and exclusion criteria, 4557 participants with MCI were included in the final analysis (Figure 1). The mean follow-up duration was 68.7 ± 32.5 months. Of these, 4133 (90.69%) remained stable without progression to AD, while 424 (9.31%) progressed from MCI to AD.

Baseline characteristics are summarized in Table 1. No significant differences were observed in age (mean: 77.9 ± 9.1 years in non-progressors vs. 77.3 ± 6.5 years in progressors; p value = 0.186) or sex distribution (63.66% women in non-progressors vs. 65.57% in progressors; p value = 0.436) between groups. Notably, polypharmacy was significantly more prevalent among non-progressors (51.05% vs. 37.03%; p value < 0.001).

Additionally, using only 1 drug and using ≥ 10 drugs was more frequent among participants without progression to AD (11.71% vs. 17.92; p value < 0.001 and 11.44% vs. 6.84%; p value = 0.004, respectively). Antipsychotics, anxiolytics, hypnotics, antidepressants, and antidementia drugs were also more frequent among individuals who did not progress to AD (Table 1).

3.2 | Impact of polypharmacy in the evolution to AD

Polypharmacy may be associated with reduced likelihood of progression from MCI to AD. In Cox proportional hazards models adjusted for age and sex, polypharmacy conferred a 76% lower hazard (HR 0.24, 95% CI: 0.19, 0.29; p value < 0.001) compared to non-polypharmacy (Table 2). This effect persisted in sex-stratified analyses, with HRs of 0.23 (95% CI: 0.18, 0.29; p value < 0.001) in women and 0.25 (95% CI: 0.18, 0.36; p value < 0.001) in men (both adjusted for age). However, the interaction between polypharmacy and sex was not statistically significant (Table S1 in supporting information).

Kaplan–Meier survival curves illustrated that polypharmacy users exhibited higher AD-free survival probability compared to non-polypharmacy participants (Figure 2).

Further analyses revealed that compared to monotherapy (one drug, reference), increasing medication count may lower HRs. This also happened when stratifying by sex, except for the usage of two drugs in women (Figure 3 and Table S2 in supporting information). The corresponding sex-stratified distribution of participants across groups is provided in Table S3 in supporting information. Nevertheless, the interaction between sex and the number of drugs was not statistically significant (Table S1).

TABLE 1 Baseline characteristics in individuals with evolution from MCI to AD versus participants without evolution.

Variables	MCI without progression (n = 4133)	MCI to AD (n = 424)	p value
Age			
Mean ± SD	77.9 ± 9.1	77.3 ± 6.5	0.186
Sex			
Women	2631 (63.66)	278 (65.57)	0.436
Men	1502 (36.34)	146 (34.43)	
Polypharmacy			
Yes	2110 (51.05)	157 (37.03)	<0.001
No	2023 (48.95)	267 (62.97)	
Number of drugs			
1 drug	484 (11.71)	76 (17.92)	<0.001
2 drugs	508 (12.29)	79 (18.63)	<0.001
3 drugs	512 (12.39)	63 (14.86)	0.145
4 drugs	519 (15.56)	49 (11.56)	0.029
5 drugs	458 (11.08)	40 (9.43)	0.300
6 drugs	398 (9.63)	32 (7.55)	0.163
7 drugs	337 (8.15)	23 (5.42)	0.047
8 drugs	255 (6.17)	20 (4.72)	0.233
9 drugs	189 (4.57)	13 (3.07)	0.153
≥ 10 drugs	473 (11.44)	29 (6.84)	0.004
Type of drugs			
Antidiabetics			
Yes	1158 (28.02)	112 (26.42)	0.483
No	2975 (71.98)	312 (73.58)	
Antithrombotics			
Yes	1858 (44.96)	192 (45.28)	0.897
No	2275 (55.04)	232 (54.72)	
Antihypertensives			
Yes	2040 (49.36)	212 (50.00)	0.802
No	2093 (50.64)	212 (50.00)	
Lipid-modifying agents			
Yes	750 (18.15)	74 (17.45)	0.724
No	3383 (81.85)	350 (82.55)	
Antipsychotics			
Yes	689 (16.67)	36 (8.49)	<0.001
No	3444 (83.33)	388 (91.51)	
Anxiolytics			
Yes	1458 (35.28)	122 (28.77)	0.007
No	2675 (64.72)	302 (71.23)	
Hypnotics and sedatives			
Yes	610 (14.76)	44 (10.38)	0.014
No	3523 (85.24)	380 (89.62)	

(Continues)

TABLE 1 (Continued)

Variables	MCI without progression ($n = 4133$)	MCI to AD ($n = 424$)	p value
Antidepressants			
Yes	1868 (45.20)	143 (33.73)	<0.001
No	2265 (54.80)	281 (66.27)	
Antidementia drugs			
Yes	1774 (42.92)	101 (23.82)	<0.001
No	2359 (57.08)	323 (76.18)	

Note: Statistical tests: chi-squared test for categorical variables represented as number (proportion, %). Continuous variables were compared using *t* test (mean ± standard deviation). p value < 0.05.
Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; SD, standard deviation.

3.2.1 | Contribution of specific drug classes

Therapeutic subclass analyses revealed that cardiovascular and psychiatric drug groups might be associated with lower probabilities of progression from MCI to AD (Figure 4 and Table S4 in supporting information). For reference, detailed sex-stratified descriptive analyses of participant distribution and progression events for each drug class are presented in Table S5 in supporting information. Furthermore, although the interaction between sex and the specific drug classes was not statistically significant (Table S1), there were differences in sex-stratified analyses.

Within cardiovascular treatments, the outcomes showed that exposure to these drug classes may be associated with a lower likelihood of progression from MCI to AD. Antidiabetic and antithrombotic agents both showed statistically significant reductions at the population level (antidiabetics: [HR 0.77, 95% CI: 0.62, 0.96; p value = 0.031]; antithrombotics: [HR 0.81, 95% CI: 0.66, 0.98; p value = 0.040]) and in women (antidiabetics: [HR 0.68, 95% CI: 0.51, 0.90; p value = 0.017]; antithrombotics: [HR 0.75, 95% CI: 0.58, 0.95; p value = 0.028]), whereas in men the estimates were not statistically significant (antidiabetics: [HR 0.95, 95% CI: 0.66, 1.36; p value = 0.769]; antithrombotics: [HR 0.88, 95% CI: 0.63, 1.23; p value = 0.572]). Similarly, antihypertensives and lipid-modifying agents also lowered the likelihood of transitioning to AD in the overall sample (antihypertensives: [HR 0.73, 95% CI: 0.60, 0.89; p value = 0.003]; lipid-modifying agents: [HR 0.75, 95% CI: 0.58, 0.97; p value = 0.040]). However, when stratifying by sex, the use of antihypertensives was only significant for men (men: [HR 0.64, 95% CI: 0.46, 0.90; p value = 0.035]; women: [HR 0.78, 95% CI: 0.61, 0.99; p value = 0.055]) and the intake of lipid-modifying agents lost significance in both sexes (men: [HR 0.60, 95% CI: 0.37, 0.95; p value = 0.062]; women: [HR 0.85, 95% CI: 0.63, 1.15; p value = 0.331]).

Regarding neuropsychiatric medications, these may have inverse associations with progression. Antipsychotics, anxiolytics, and antidementia drugs might be linked to lower hazards of conversion in the overall cohort (antipsychotics: [HR 0.54, 95% CI: 0.38, 0.76; p value = 0.001]; anxiolytics: [HR 0.64, 95% CI: 0.51, 0.79; p value < 0.001]; antidementia: [HR 0.44, 95% CI: 0.35, 0.55; p value < 0.001]), with similar patterns in women (antipsychotics: [HR 0.59, 95% CI: 0.39, 0.89; p value = 0.019]; anxiolytics: [HR 0.71, 95% CI: 0.55, 0.92; p value = 0.017]; antidementia: [HR 0.41, 95% CI: 0.29, 0.54; p value < 0.001]) and men (antipsychotics: [HR 0.45, 95% CI: 0.24, 0.87; p value = 0.044]; anxiolytics: [HR 0.50, 95% CI: 0.33, 0.76; p value = 0.005]; antidementia: [HR 0.49, 95% CI: 0.33, 0.72; p value = 0.002]). Hypnotics and sedatives (overall: [HR 0.59, 95% CI: 0.43, 0.81; p value = 0.002]; women: [HR 0.60, 95% CI: 0.42, 0.87; p value = 0.017]) and antidepressants (overall: [HR 0.55, 95% CI: 0.45, 0.68; p value < 0.001]; women: [HR 0.50, 95% CI: 0.39, 0.64; p value < 0.001]) may be associated with lower probabilities of developing AD; however, this was not statistically significant in men (hypnotics and sedatives: [HR 0.56, 95% CI: 0.31, 1.02; p value = 0.080]; antidepressants: [HR 0.68, 95% CI: 0.48, 0.98; p value = 0.065]).

4 | DISCUSSION

This longitudinal study conducted in 4557 participants examined the association among polypharmacy, medication burden, and progression from MCI to AD. The outcomes suggest that higher medication burden may be linked to a lower likelihood of conversion from MCI to AD, with lower HRs as the number of concomitant drugs increased. At the same time, although no statistically significant interaction between sex and medication use was observed, sex-stratified analyses might suggest some differences: antidiabetic, antithrombotic, sedative, and antidepressant therapies may be associated with reduced likelihood of MCI to AD conversion predominantly in women, antihypertensive treatment showed statistically significantly lower HRs mainly in men, and antipsychotics, anxiolytics, and antidementia drugs were associated with lower progression rates in both sexes.

Polypharmacy has traditionally been regarded as detrimental in the context of cognitive impairment and dementia.[5,23–26] However, our findings suggest that polypharmacy may be observationally associated with a lower likelihood of progression to AD. This is consistent with recent evidence indicating that polypharmacy can be associated with a lower risk of progression to dementia among people with MCI.[28] It is important to acknowledge that higher polypharmacy is often associated with a higher risk of mortality in elder people.[29] Therefore, our results may be subject to competing risks, as some polymedicated patients might have died before an AD diagnosis could be established.

To explore which pharmacological domains may underlie the association between polypharmacy and the conversion from MCI to AD, we evaluated cardiovascular and psychiatric drug classes, which are two therapeutic areas closely related to some of the main risk factors for AD.[10] It is noteworthy that all analyzed medications were associated with a lower likelihood of progression to AD.

While comorbidities such as diabetes,[36–38] hypertension,[33,39] dyslipidemia,[40,41] and psychiatric comorbidities (depression, anxiety, and insomnia)[15] may increase the risk of cognitive decline, effective management through pharmacological treatment may help preserve cognitive function.[33,42–46] In Spain, the Ministry of Health published

TABLE 2 Hazard ratios with 95% confidence intervals (CIs) of the association of polypharmacy and the likelihood of progression from mild cognitive impairment to Alzheimer's disease in the overall sample and stratifying by sex.

	Overall		Women		Men	
Variables	**HRs (95% CIs)**	***p* value**	**HRs (95% CIs)**	***p* value**	**HRs (95% CIs)**	***p* value**
Polypharmacy						
No	Reference		Reference		Reference	
Yes	0.24 (0.19, 0.29)	<0.001	0.23 (0.18, 0.29)	<0.001	0.25 (0.18, 0.36)	<0.001

Note: p value < 0.05.
Statistical tests: Cox proportional hazard ratios.

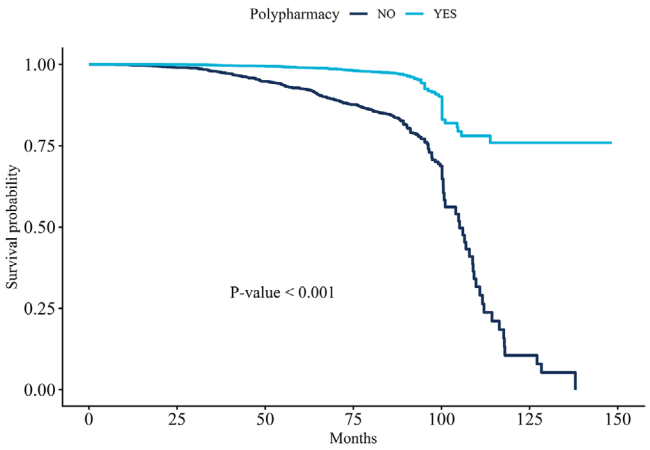


FIGURE 2 Survival probability without progression from mild cognitive impairment to Alzheimer's disease according to polypharmacy status.

clinical guidelines in which the intensive monitoring of polymedicated patients was a priority,[47] suggesting that this closer clinical follow-up may result in optimal management of these chronic comorbidities. Consequently, the magnitude and consistency of the inverse associations observed across almost all medication classes strongly point to limited covariate adjustment and the absence of comorbidity information. Therefore, our findings likely reflect the effects of underlying health-care use and comorbidities rather than pharmacological effects per se.

Regarding sex analyses, although interaction analyses were not statistically significant, sex-stratified analyses suggested some differences. No sex differences were observed in the prevalence of polypharmacy or in the number of drugs taken. However, some medications may be associated with a lower likelihood of AD predominantly in one sex: antidiabetics, antithrombotics, hypnotics, sedatives, and antidepressants in women, and antihypertensives in men.

Even in the absence of a significant statistical interaction, the differences observed in sex-stratified analyses could reflect sex-specific disease biology, variations in pharmacokinetics or pharmacodynamics, or differential prescribing practices.[5] For instance, sex differences in insulin sensitivity,[48,49] in controlling vascular risk factors,[50] and in comorbidity prevalence[4] might contribute to the diverse drug responses observed.

Similarly, antidementia drugs, anxiolytics, and antipsychotics might be associated with lower conversion of MCI to AD in both sexes. While antidementia drugs target cholinergic[4] and glutaminergic pathways,[51] antipsychotics[26] and anxiolytics[26,52] are often prescribed to manage behavioral and psychological symptoms, which are common in people with cognitive impairment and AD.[53] Notably, our findings regarding psychotic medications contrast with previous studies suggesting an increase in the likelihood of AD diagnosis in people with MCI.[3]

However, the data do not allow to stablish a direct pharmacological mechanism and, therefore, these findings must be interpreted strictly as hypothesis-generating. These associations may reflect underlying patient characteristics, health-care use, or selection bias rather than true protective effects of medications.

In conclusion, this real-world study suggests that, in older adults with MCI, higher medication burden may be associated with a lower likelihood of progression to AD. Notably, sex-stratified analyses revealed distinct patterns: antidiabetics, antithrombotics, hypnotics, sedatives, and antidepressants may be associated with lower AD progression in women, whereas antihypertensives might be linked to reduced progression in men. These results highlight the importance of considering sex-specific associations in pharmacological effects on cognitive trajectories, but they should be interpreted cautiously, especially because formal interaction analyses did not show statistically significant differences.

Given the observational nature of the study, these associations cannot establish causality and may reflect underlying comorbidities, differences in health-care follow-up, or confounding by indication rather than a direct protective effect of polypharmacy itself. Therefore, these results should not be interpreted as evidence of a beneficial clinical effect of polypharmacy, but rather as hypothesis generating about possible pharmacological influences on MCI progression and sex-specific patterns. Further prospective studies are required to confirm these associations and to explore safe, sex-informed strategies for managing comorbidities in individuals with MCI.

4.1 | Strengths and limitations

The main strengths of this study are its large sample size, longitudinal design, and the use of ICD-10-CM codes for diagnosing neurodegenerative disorders.

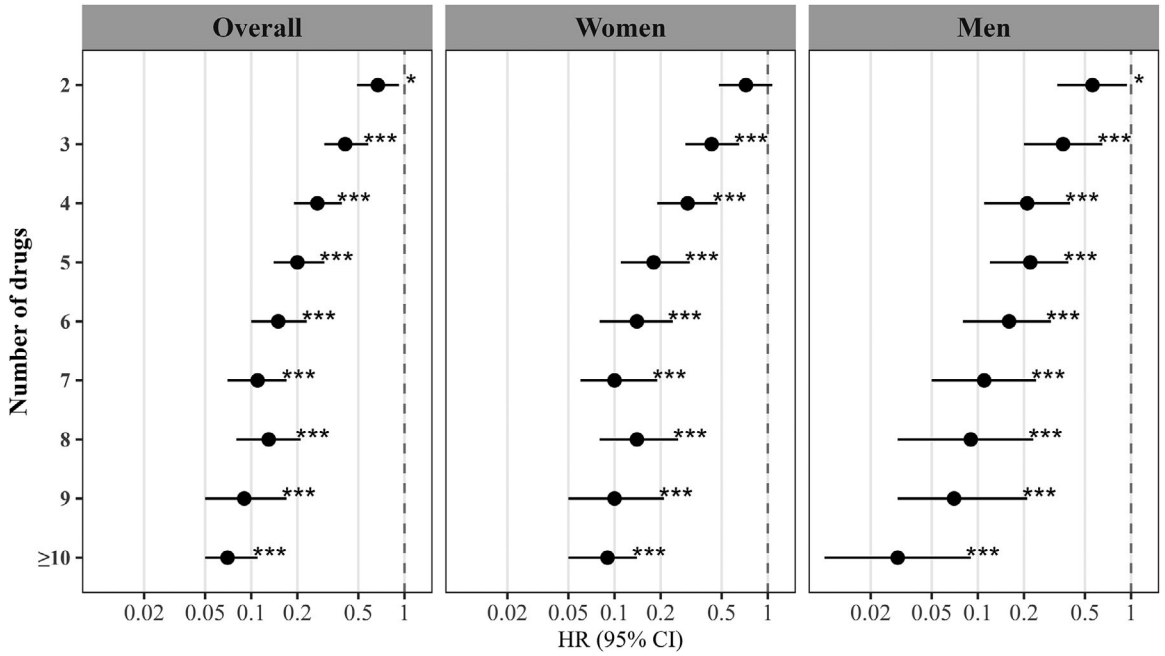


FIGURE 3 Forest plot showing HRs and 95% CIs for the association between the total number of concomitant medications and the likelihood of transitioning from MCI to AD in the overall sample and stratified by sex. The number of drugs was modeled categorically, with one medication as the reference category. The overall model was adjusted for age and sex; models for women and men were adjusted for age. *p* value < 0.001 ***, < 0.01 **, < 0.05 *; FDR adjusted. AD, Alzheimer's disease; CI, confidence interval; FDR, false discovery rate; HR, hazard ratio; MCI, mild cognitive impairment.

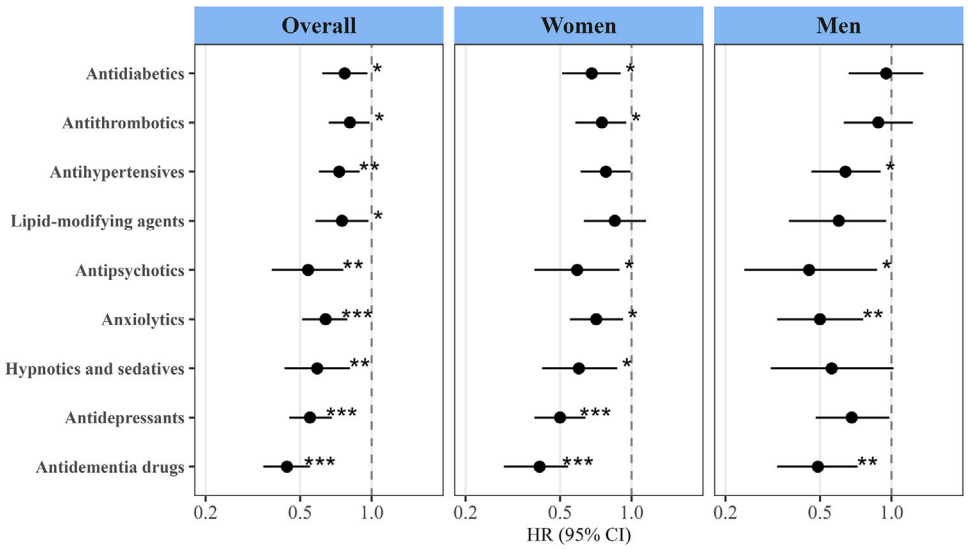


FIGURE 4 Forest plot showing HRs and 95% CIs for the association between the likelihood of transitioning from MCI to AD according to drug groups, in the overall sample and stratified by sex. The overall model was adjusted for age and sex; models for women and men were adjusted for age. *p* value < 0.001 ***, < 0.01 **, < 0.05 *; FDR adjusted. AD, Alzheimer's disease; CI, confidence interval; FDR, false discovery rate; HR, hazard ratio; MCI, mild cognitive impairment.

However, several limitations should be acknowledged. First, drug exposure was inferred from prescriptions, without information on adherence. Second, we only had access to age and sex as covariates; detailed data on other comorbidities, lifestyle, or socioeconomic factors were unavailable, which may limit adjustment for potential confounding. Third, follow-up did not include mortality data, potentially introducing bias. Fourth, medication exposure, including polypharmacy, was treated as a baseline variable, and we did not observe

changes over time; polypharmacy is inherently dynamic, and time-varying patterns may influence outcomes. Fifth, while multivariate models included multiple drug classes to adjust each class for concomitant medication use, we did not have data on the underlying comorbidities; therefore, associations with individual drug classes should be interpreted as descriptive rather than causal. Finally, the requirement of at least 6 months of medication use prior to MCI diagnosis may introduce selection or immortal time bias, and participants on long-term therapy before cohort entry (prevalent users) may differ from those initiating treatment closer to the MCI diagnosis. In addition, we must acknowledge a potential surveillance bias, as patients receiving chronic pharmacological treatment may have more frequent medical encounters, increasing the likelihood of an earlier MCI to AD progression diagnosis compared to untreated individuals.

Despite these limitations, longitudinal studies of this nature have the capacity to furnish valuable insights into the relationship between treatment usage and AD outcomes, thereby establishing new hypotheses for future studies.

ACKNOWLEDGMENTS

We thank the *Consellería de Sanitat Universal i Salut Pública* (Valencian Regional Health Authority, Spain) and PROSIGA for providing the data used in this study. This research was funded by the grant number INDI25/17 and GIR25/14 from the Universidad CEU Cardenal Herrera, Spain. Ayudas a la formación de jóvenes investigadores SANTANDER-CEU.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT

Consent was not necessary.

ORCID

Juan Pardo https://orcid.org/0000-0003-4184-9855

REFERENCES

1. World Health Organization (WHO). Dementia. World Health Organization; 2025 (cited 2024 Sep 23). Accessed 23 Sep 2024. https://www.who.int/news-room/fact-sheets/detail/dementia
2. Davis M, O'Connell T, Johnson S, et al. Estimating Alzheimer's disease progression rates from normal cognition through mild cognitive impairment and stages of dementia. *Curr Alzheimer Res*. 2018;15:777-788. doi:10.2174/1567205015666180119092427
3. Potashman M, Parcher B, Zhou J, Hou Q, Stefanacci R. Identification of cognitively impaired patients at risk for development of Alzheimer's disease dementia: an analysis of US Medicare claims data. *Expert Rev Pharmacoecon Outcomes Res*. 2022;22:773-786. doi:10.1080/14737167.2022.2045956
4. Efjestad AS, Ihle-Hansen H, Hjellvik V, Engedal K, Salvesen Blix H. Sex differences in psychotropic and analgesic drug use before and after initiating treatment with acetylcholinesterase inhibitors. *PLoS One*. 2021;16:e0243804. doi:10.1371/journal.pone.0243804
5. Eroli F, Johnell K, Acararicin Z, Tsagkogianni C, Zerial S, Lancia S, et al. Commonly prescribed multi-medication therapies exert sex-specific effects on Alzheimer's disease pathology and metabolomic profiles in App^{NL-G-F} mice: implications for personalized therapeutics in aging. *Alzheimers Dement*. 2025;21:e70081. doi:10.1002/alz.70081
6. Defrancesco M, Marksteiner J, Kemmler G, Fleischhacker WW, Blasko I, Deisenhammer EA. Severity of depression impacts imminent conversion from mild cognitive impairment to Alzheimer's disease. *J Alzheimers Dis*. 2017;59:1439-1448. doi:10.3233/JAD-161135
7. Ding X, Yin L, Zhang L, et al. Diabetes accelerates Alzheimer's disease progression in the first year post mild cognitive impairment diagnosis. *Alzheimers Dement*. 2024;20:4583-4593. doi:10.1002/alz.13882
8. Deng Z, Jiang J, Wang J, et al. Angiotensin receptor blockers are associated with a lower risk of progression from mild cognitive impairment to dementia. *Hypertension*. 2022;79:2159-2169. doi:10.1161/HYPERTENSIONAHA.122.19378
9. Bartels C, Wagner M, Wolfsgruber S, Ehrenreich H, Schneider A. Impact of SSRI therapy on risk of conversion from mild cognitive impairment to Alzheimer's dementia in individuals with previous depression. *Am J Psychiatry*. 2018;175:232-241. doi:10.1176/appi.ajp.2017.17040404
10. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing commission. *Lancet*. 2024;404:572-628. doi:10.1016/S0140-6736(24)01296-0
11. Chêne G, Beiser A, Au R, Preis SR, Wolf PA, Dufouil C, et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimers Dement*. 2015;11:310-320. doi:10.1016/j.jalz.2013.10.005
12. Nooyens ACJ, Wijnhoven HAH, et al. Sex differences in cognitive functioning with aging in the Netherlands. *Gerontology*. 2022;68:999-1009. doi:10.1159/000520318
13. Eastman J, Bahorik A, Kornblith E, Xia F, Yaffe K. Sex differences in the risk of dementia in older veterans. *J Gerontol A Biol Sci Med Sci*. 2022;77:1250-1253. doi:10.1093/gerona/glac029
14. Levine DA, Gross AL, Briceño EM, et al. Sex differences in cognitive decline among US adults. *JAMA Netw Open*. 2021;4:e210169. doi:10.1001/jamanetworkopen.2021.0169
15. Gil-Peinado M, Alacreu M, Ramos H, et al. The A-to-Z factors associated with cognitive impairment. Results of the DeCo study. *Front Psychol*. 2023;14:1152527. doi:10.3389/fpsyg.2023.1152527
16. Lopez-Lee C, Torres ERS, Carling G, Gan L. Mechanisms of sex differences in Alzheimer's disease. *Neuron*. 2024;112:1208-1221. doi:10.1016/j.neuron.2024.01.024
17. Arenaza-Urquijo EM, Boyle R, Casaletto K, et al. Sex and gender differences in cognitive resilience to aging and Alzheimer's disease. *Alzheimers Dement*. 2024;20:5695-5719. doi:10.1002/alz.13844
18. Aggarwal NT, Mielke MM. Sex differences in Alzheimer's disease. *Neurol Clin*. 2023;41:343-358. doi:10.1016/j.ncl.2023.01.001
19. Schweitzer N, Son SJ, Thurston RC, et al. Sex-specific risk factors and clinical dementia outcomes for white matter hyperintensities in a large South Korean cohort. *Alzheimers Res Ther*. 2024;16:243. doi:10.21203/rs.3.rs-4473148/v1
20. Wood Alexander M, Paterson J, Arvanitakis Z, Black SE, Casaletto KB, Christakis MK. Cardiovascular contributions to dementia: examining sex differences and female-specific factors. *Alzheimers Dement*. 2025;21:e70610. doi:10.1002/alz.70610
21. Kaur A, Fouad MH, Pozzebon C, Behlouli H, Rajah MN, Pilote L. Sex differences in the association between vascular risk factors and cognitive decline. *JACC Adv*. 2024;3:100930. doi:10.1016/j.jacadv.2024.100930
22. Francesca E, Kristina J, María L-L, et al. Long-term exposure to polypharmacy impairs cognitive functions in young adult female mice. *Aging*. 2021;13:14729-14744. doi:10.18632/aging.203132
23. Du L, Koscik RL, Chin NA, et al. Prescription medications and comorbidities in late middle-age are associated with greater cognitive declines: results from WRAP. *Front Aging*. 2022;2:759695. doi:10.3389/fragi.2021.759695

24. Trevisan C, Limongi F, Siviero P, et al. Mild polypharmacy and MCI progression in older adults: the mediation effect of drug–drug interactions. *Aging Clin Exp Res*. 2021;33:49-56. doi:10.1007/s40520-019-01420-2
25. Clague F, Mercer SW, McLean G, Reynish E, Guthrie B. Comorbidity and polypharmacy in people with dementia: insights from a large, population-based cross-sectional analysis of primary care data. *Age Ageing*. 2016;46(1):33-39. doi:10.1093/ageing/afw176
26. Parsons C. Polypharmacy and inappropriate medication use in patients with dementia: an underresearched problem. *Ther Adv Drug Saf*. 2017;8:31-46. doi:10.1177/2042098616670798
27. Soysal P, Perera G, Isik AT, et al. The relationship between polypharmacy and trajectories of cognitive decline in people with dementia: a large representative cohort study. *Exp Gerontol*. 2019;120:62-67. doi:10.1016/j.exger.2019.02.019
28. Hsu Y, Liang C, Chou M, et al. Polypharmacy and risk of dementia progression in older adults with mild cognitive impairment: a longitudinal cohort study. *Alzheimers Dement*. 2025;11:e70179. doi:10.1002/trc2.70179
29. Li Y, Zhang X, Yang L, et al. Association between polypharmacy and mortality in the older adults: a systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2022;100:104630. doi:10.1016/j.archger.2022.104630
30. Morales J, Gabriel N, Natarajan L, et al. Pharmacoepidemiology evaluation of bumetanide as a potential candidate for drug repurposing for Alzheimer's disease. *Alzheimers Dement*. 2024;20:5236-5246. doi:10.1002/alz.13872
31. Poblano J, Castillo-Tobías I, Berlanga L et al., et al. Drugs targeting APOE4 that regulate beta-amyloid aggregation in the brain: therapeutic potential for Alzheimer's disease. *Basic Clin Pharmacol Toxicol*. 2024;135:237-249. doi:10.1111/bcpt.14055
32. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guideline. 1992.
33. Ding M, Wennberg AM, Engström G, Modig K. Use of common cardiovascular disease drugs and risk of dementia: a case–control study in Swedish national register data. *Alzheimers Dement*. 2025;21:e14389. doi:10.1002/alz.14389
34. Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ*. 2018;367:k1315. doi:10.1136/bmj.k1315
35. Posit Software PBM. Posit team. RStudio: Integrated Development Environment for R. (cited 2026 Apr 17) Accessed 17 Apr 2026. 2025. http://www.posit.co/
36. Nguyen TT, Ta QTH, Nguyen TKO, Nguyen TTD, Van Giau V. Type 3 diabetes and its role implications in Alzheimer's disease. *Int J Mol Sci*. 2020;21:3165. doi:10.3390/ijms21093165
37. Michailidis M, Moraitou D, Tata DA, Kalinderi K, Papamitsou T, Papaliagkas V. Alzheimer's disease as type 3 diabetes: common pathophysiological mechanisms between Alzheimer's disease and type 2 diabetes. *Int J Mol Sci*. 2022;23:2687. doi:10.3390/ijms23052687
38. Barone E, Di Domenico F, Perluigi M, Butterfield DA. The interplay among oxidative stress, brain insulin resistance and AMPK dysfunction contribute to neurodegeneration in type 2 diabetes and Alzheimer disease. *Free Radic Biol Med*. 2021;176:16-33. doi:10.1016/j.freeradbiomed.2021.09.006
39. Colombari E, Biancardi VC, Colombari DSA, et al. Hypertension, blood–brain barrier disruption and changes in intracranial pressure. *J Physiol*. 2025;603:2245-2261. doi:10.1113/JP285058
40. Petek B, Häbel H, Xu H, et al. Statins and cognitive decline in patients with Alzheimer's and mixed dementia: a longitudinal registry-based cohort study. *Alzheimers Res Ther*. 2023;15:220. doi:10.1186/s13195-023-01360-0
41. Kao Y-C, Ho P-C, Tu Y-K, Jou I-M, Tsai K-J. Lipids and Alzheimer's Disease. *Int J Mol Sci*. 2020;21:1505. doi:10.3390/ijms21041505
42. Zamora MG, García-Lluch G, Moreno L, Pardo J, Pericas CC. Assessment of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and other antidiabetic agents in Alzheimer's disease: a population-based study. *Pharmacol Res*. 2024;206:107295. doi:10.1016/j.phrs.2024.107295
43. García-Zamora M, García-Lluch G, Moreno L, Pardo J, Cháfer–Pericás C. Influence of statin potency and liposolubility on Alzheimer's disease patients: a population-based study. *Pharmacol Res*. 2024;209:107446. doi:10.1016/j.phrs.2024.107446
44. Ding J, Davis-Plourde KL, Sedaghat S, et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol*. 2020;19:61-70. doi:10.1016/S1474-4422(19)30393-X
45. Kuate Defo A, Bakula V, Pisaturo A, Labos C, Wing SS, Daskalopoulou SS. Diabetes, antidiabetic medications and risk of dementia: a systematic umbrella review and meta-analysis. *Diabetes Obes Metab*. 2024;26:441-462. doi:10.1111/dom.15331
46. Gil-Peinado M, Pardo J, García-Zamora M, Adsuar-Meseguer GM, Sendra-Lillo J, Moreno L. Evaluating the rational use of antidepressant in older patients: a comprehensive analysis of its association with cognitive impairment. *Front Psychiatry*. 2025;16:1624989. doi:10.3389/fpsyt.2025.1624989
47. Spanish Ministry of Health. Recomendaciones sobre conciliación de la medicación en atención primaria en pacienets crónicos. 2022.
48. Cholerton B, Baker LD, Trittschuh EH, et al. Insulin and sex interactions in older adults with mild cognitive impairment. *J Alzheimers Dis*. 2012;31:401-410. doi:10.3233/JAD-2012-120202
49. Gil-Bea FJ, Solas M, Solomon A, et al. Insulin levels are decreased in the cerebrospinal fluid of women with prodomal Alzheimer's disease. *J Alzheimers Dis*. 2010;22:405-413. doi:10.3233/JAD-2010-100795
50. Morrison C, Dadar M, Collins DL. Sex differences in risk factors, burden, and outcomes of cerebrovascular disease in Alzheimer's disease populations. *Alzheimers Dement*. 2024;20:34-46. doi:10.1002/alz.13452
51. Kim AY, Al Jerdi S, MacDonald R, Triggle CR. Alzheimer's disease and its treatment–yesterday, today, and tomorrow. *Front Pharmacol*. 2024;15:1399121. doi:10.3389/fphar.2024.1399121
52. Kaur DP, Bucholc M, Finn DP, Todd S, Wong-Lin KF, McClean PL. Impact of different diagnostic measures on drug class association with dementia progression risk: a longitudinal prospective cohort study. *J Alzheimers Dis*. 2024;100:631-644. doi:10.3233/JAD-230456
53. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules*. 2020;25:5789. doi:10.3390/molecules25245789

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: García-Zamora M, Pardo J, Esteve M, Martinez-Gracia A, Cháfer-Pericás C, Falcó A. Polypharmacy is associated with lower progression from MCI to Alzheimer's disease, with sex-specific patterns across drug classes. *Alzheimer's Dement*. 2026;18:e70379. https://doi.org/10.1002/dad2.70379