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Ten-Year Trajectory of Potentially Inappropriate Medications in Very Old Women: Importance of Cognitive Status

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	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Employment or Affiliation		x		x		x		x		x
Grants/Funds		x		x		x		x		x
Honoraria		x		x		x		x		x
Speaker Forum		x		x		x		x		x
Consultant		x		x		x		x	x	
Stocks		x		x		x		x		x
Royalties		x		x		x		x		x
Expert Testimony		x		x		x		x		x
Board Member		x		x		x		x		x
Patents		x		x		x		x		x
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Study concept and design (AK, MS, KY), acquisition of subjects and/or data (AK, KE, TH, KY), analysis and interpretation of data (AK, MS, KE, TH, KY), and preparation of manuscript (AK, MS, KE, TH, KY).

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Abstract

Background/ Objectives—Older populations are particularly susceptible to adverse effects from potentially inappropriate medications (PIMs), which can be associated with cognitive impairment. Additionally, many older adults have existing cognitive impairment which can be exacerbated by PIMs. It is not clear which older adults tend to receive PIMs, how this may differ by cognitive status, or how the trajectories of PIM use change over time.

Design—Longitudinal cohort study

Setting—Three clinical sites in the United States.

Participants—We followed 1,484 community-dwelling women ≥ 75 years of age over 10 years.

Measurements—At follow-up, we ascertained cognitive status, which was classified as normal, mild cognitive impairment (MCI) or dementia. Beers 2003 criteria and other literature were used to identify PIMs from detailed medication inventory performed at three time points. We also measured anticholinergic load using the Anticholinergic Cognitive Burden scale (ACB), which assigns medications a value from 0 to 3 depending on anticholinergic properties.

Results—At baseline, 23.9% of women were taking at least one PIM and the mean(± SD) ACB score was 1.41(± 1.69). The most frequently reported PIMs were anticholinergics (15.2%), benzodiazepines (8.6%), and antispasmodics (8.0%). Over 10 years, PIM use increased for women with dementia (24.9% to 33.1%; p=0.02), yet remained fairly constant for women with MCI (23.9% to 23.0%; p=0.84) and normal cognitive status (22.2% to 19.8%; p=0.17). Mean ACB score significantly increased (p<0.001) over time for all groups (dementia: 1.28 to 2.05; MCI: 0.98 to 1.66; normal: 0.99 to 1.48).

Conclusion—PIM use and anticholinergic load in a community-dwelling population of older women is high, especially among women who later develop dementia. Future guidelines should limit PIM use and seek safer alternatives.

Keywords

cognitive function; dementia; potentially inappropriate medication; anticholinergic

Introduction

Because of increasing comorbidities, frequent medication use is common in elderly populations. Although medications can provide an effective therapeutic benefit, some can also be considered potentially inappropriate medications (PIMs), defined by expert consensus to be problematic in older adults because of limited effectiveness and/or troublesome adverse effect profiles[1]. Many PIMs can contribute to other comorbidities and impair cognitive function[1]. Age-related changes in pharmacokinetics and pharmacodynamics can also contribute to potentially harmful adverse effects, and multiple medication use can lead to drug-drug and drug disease interactions[2]. Despite existing guidelines to limit their use[1, 3], PIM use remains common in older populations. Randomized clinical trials have shown that guidelines on PIM use, when implemented by physicians or pharmacists, can significantly reduce the number of prescribed PIMs[4, 5]. Regardless, studies consistently show that a significant proportion of elderly patients with or without cognitive impairment are prescribed PIMs[6, 7].

The majority of existing studies have examined PIM use in a cross-sectional design or in relation to functional outcomes. In contrast, less is known about how PIM use changes over time, especially by cognitive status. It is possible that PIM use is associated with cognitive decline as a cause, consequence, or both. As individuals with cognitive impairment are a particularly vulnerable population, it is important to know more about their profile of PIM use. Therefore, we examined the trajectories of PIM use by cognitive status at follow-up in older women into their eighth and ninth decades of life. As anticholinergics are found to be associated with cognitive impairment[8], we also examined the trajectories of anticholinergic load. Lastly, we aimed to determine what characteristics among oldest old women are associated with PIM use.

Methods

Study Participants

Study participants were women enrolled in the Study of Osteoporotic Fractures (SOF), a multi-center, prospective study of women 65 years and over at baseline[9]. In brief, from 1986 to 1988, community-dwelling women who were able to walk were recruited via mailing lists from four sites in the United States (Minneapolis, Minnesota; Portland, Oregon; Baltimore, Maryland; Monongahela Valley, Pennsylvania). The initial cohort consisted of a majority of Caucasian women (99.7%). From 1997 to 1998, a cohort of 662 African-American women was added.

We studied women in an ancillary study of clinical cognitive status, in which three of the four original sites participated (Baltimore did not participate). Medication inventory began from 1997 to 1998 and is therefore used as the baseline time point for the present study. Follow-up visits occurred approximately 6 (2002–2004) and 10 years later (2006–2008). As we intended to examine PIM use over 10 years, our analytic cohort comprised women with both medication inventory at each time point and cognitive status at follow-up. Of the 5,672 women enrolled at baseline, 3,135 died and 1,053 had incomplete medication inventory, withdrew from the study, or were lost to follow-up, resulting in an analytic cohort of 1,484 women. Women who did not remain in the study were more likely to be older ($p<0.001$), have fewer years of education ($p<0.001$) and more comorbidities ($p<0.001$). This study was approved by an institutional review board (University of California, San Francisco) and written informed consent was obtained from all participants in the study.

Participant Characteristics

At each visit, age and other anthropometric measures such as body mass index (BMI) were calculated. Lifestyle factors were recorded via questionnaire, including physical activity and smoking history. Women were also asked if a physician ever diagnosed them for medical conditions, including dementia or Alzheimer's disease (AD), cancer, congestive heart failure, chronic obstructive pulmonary disease (COPD), type 2 diabetes, myocardial infarction (MI), hypertension, osteoarthritis, stroke, and urinary incontinence. Depression and anxiety were measured using the Geriatric Depression Scale (GDS) and Goldberg Anxiety Scale, respectively. Both scales are brief questionnaires requiring yes or no responses to basic questions regarding common symptoms of depression or anxiety. Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), a questionnaire designed to measure several aspects of sleep quality, use of sleep medications, and daytime dysfunction. Trained interviewers measured cognitive function using the Mini-Mental State Examination (MMSE) at baseline and at the 6-year follow-up. At the 10-year follow-up, MMSE score was derived from the modified Mini-Mental State Examination (3MS). Medication inventory was classified using the Iowa Drug Information System (IDIS) coding[10]. At each time point, women were instructed to bring in all prescription medications

used within the past 30 days. At baseline and at 10 years, women were also asked to bring in select over-the-counter (OTC) medications or fill out a questionnaire on OTC use. A complete inventory of OTC medication was done at the 6-year time point.

Outcome assessment

The primary outcome of interest was the number of PIMs reported at each time point. To focus on medications with known cognitive effects, a medication was considered a PIM if it was classified as such for older adults with cognitive impairment according to the 2003 Beers criteria[1]. These medication classes included barbiturates, anticholinergics, antispasmodics, muscle relaxants, and central nervous system (CNS) stimulants. In addition, benzodiazepines and sedative-hypnotics were added to this list as previous literature has indicated these classes of medications can contribute to cognitive impairment in older adults[11, 12]. Medications were categorized into PIM classes using standard references and existing literature[10, 12, 13]. Some medications were included in multiple classes, but were only counted once for the total number of PIMs.

A secondary outcome was the total score on the Anticholinergic Cognitive Burden Scale (ACB), a composite measure of anticholinergic load[13]. The ACB score assigns a value from 0 to 3 for a given medication. A medication is assigned a 0 if there is no anticholinergic activity, and a 1 if there is possible anticholinergic activity suggested by serum anticholinergic activity or in vitro affinity to muscarinic receptors. For medications with known clinically relevant anticholinergic effects, a 2 or 3 is given, based on the drug's ability to cross the blood-brain barrier and its association with delirium. The ACB score for each participant was computed by summing these values for each reported medication. The scale was developed through a systematic review by an interdisciplinary panel and validated in subsequent studies[8, 14].

Cognitive assessment

At the 10-year follow-up, women were evaluated and then adjudicated for clinical cognitive status through a multi-step process, which is described in detail elsewhere[15]. In brief, based on thresholds for cognitive test scores, previous dementia diagnosis, or nursing home residence, women were either considered cognitively normal or underwent additional assessment. A panel of clinical experts then adjudicated cognitive status based on cognitive test scores, functional status, medications, and medical history. Dementia diagnosis was made based on the Diagnostic and Statistical Manual of Mental Disorders (4^{th} ed.)[16]. Mild cognitive impairment (MCI) was diagnosed based on modified Petersen criteria[17]. After additional assessment, women were considered cognitively normal if they were not classified as having either MCI or dementia.

Statistical analysis

To determine if any differences existed for characteristics between PIM users and non-users, one-way ANOVA tests were used for normally distributed variables, Kruskal-Wallis tests for non-normal continuous variables, and chi-square tests for dichotomous variables. To test for differences in PIM use by cognitive status between baseline and 10-year follow-up, McNemar's tests were used. Kruskal-Wallis tests were used to make pairwise comparisons of ACB score, by cognitive status. To assess the trajectories of PIM use and ACB score over time, we used a repeated measures marginal model with an unstructured covariance pattern. We considered differences between groups at each time point, the overall effect of time, and differences in rate of change over time. Both crude models and fully adjusted models were assessed. Covariates in the fully adjusted model included any variable measured at baseline associated ($p < 0.05$) with PIM use. The final model included adjustments for age, race, education, a modified Charlson Comorbidity Index[18], GDS score, BMI, and physical

activity. All analyses were performed using SAS 9.2 software (SAS Institute, Inc., Cary, NC).

Results

Participant characteristics are detailed in Table 1. Mean(± SD) follow-up time was 9.7(± 0.6) years. At follow-up, PIM users scored higher on the GDS (p<0.001), had poor sleep quality (p<0.001), lower scores on the MMSE (p<0.001), and increased anxiety (p<0.001). PIM use was also associated with urinary incontinence (p=0.03), osteoarthritis (p=0.03), MI (p=0.02), fewer years of education (p=0.04), Caucasian race (p=0.03), and COPD (p=0.006). At baseline, 24.3% of women were PIM users, followed by 27.3% at 6 years and 23.9% at 10 years. Differences in prevalence emerged when comparing PIM use by cognitive status. For women with dementia at follow-up, the proportion of PIM users increased over the follow-up period (26.1% to 33.5%; p=0.04). In contrast, PIM use declined slightly for women with MCI at follow-up (26.1% to 24.4%; p=0.61) and for those who remained cognitively normal over the follow-up period (23.0% to 20.6%; p=0.17).

At 10 years, the most frequently used class of PIMs was anticholinergics, reported by 226 (15.2%) women. Benzodiazepines were the next most common (n=128; 8.6%), followed by antispasmodics (n=118; 8.0%), sedative-hypnotics (n=56; 3.8%), muscle relaxants (n=14; 0.9%), CNS stimulants (n=10; 0.7%), and barbiturates (n=8; 0.5%). Accounting for 75% of all reported PIMs, the most frequently reported were oxybutynin (n=57), tolterodine (n=47), lorazepam (n=43), alprazolam (n=30), paroxetine (n=28), temazepam (n=27), zolpidem (n=24), and meclizine (n=24). This profile of PIM use remained similar at previous time points, and across groups of cognitive function. At 10 years, 260 (17.5%) women had dementia, 354 (23.9%) had MCI, and 870 (58.6%) were cognitively normal.

Trajectories of PIM use

At baseline, the unadjusted mean number of PIMs reported by women was 0.36(0.04) for the dementia group, 0.36(0.03) for the MCI group, and 0.30(0.02) for those who remained cognitively normal (Table 2). Differences between groups were not significant in the unadjusted model (p=0.21), or after adjustment for age, race, education, a modified Charlson Comorbidity Index, GDS score, BMI, and physical activity (p=0.70). After 10 years of follow-up, the mean(SE) number of PIMs increased to 0.44(0.04) for the dementia group, and decreased slightly to 0.31(0.03) for the MCI group and to 0.25(0.02) for the cognitively normal group. Differences between groups at this point became significant (unadjusted p<0.001; adjusted p<0.001). The rates of change in PIM use over 10 years were significantly different between groups (unadjusted p=0.04; adjusted p=0.03). However, as seen in Figure 1, these trends were not monotonic and the overall magnitude of changes was small.

Trajectories of ACB score

Table 2 displays the predicted mean ACB score of each group of women over the 10 year follow-up period. At baseline, the unadjusted mean(SE) of ACB score was 1.39(0.11) for the dementia group, 1.17(0.09) for the MCI group, and 1.14(0.06) for the cognitively normal group. Differences in ACB score between groups were not significant at baseline (unadjusted p=0.15; adjusted p=0.19). At the 10-year follow-up, the mean(SE) ACB score increased to 2.06(0.10) for women with dementia, 1.67(0.09) for women with MCI, and 1.48(0.06) for those who remained cognitively normal. These differences were significant for both unadjusted and adjusted models (p<0.001). As shown in Figure 1, the ACB score for all groups increased for each group over the follow-up period. The difference in rate of change between groups was significant in both the unadjusted model (p=0.02) adjusted model (p=0.01).

Discussion

Results showed that rates of PIM use and anticholinergic load significantly differed based on cognitive status. At the 10-year follow-up, both increased PIM use and higher anticholinergic load were significantly associated with decreased cognitive function. In the oldest old women, PIM use was unsurprisingly associated with increased comorbidities. Psychiatric comorbidities had a particularly strong association with PIM use, a finding consistent with previous studies[12, 19]. The most frequently reported PIMs in this cohort included anticholinergic antispasmodics used for urinary incontinence and benzodiazepines. The frequent use of benzodiazepines can be attributed to the higher prevalence of insomnia and anxiety in the elderly[20, 21]. However, it may also be due to an age-cohort effect, as many of the women lived during an era when the adverse effects of benzodiazepines were not yet evident.

Interestingly, although each cognitive group differed in their changes of PIM use, ACB score significantly increased for all three groups. The increase in anticholinergic medication is of particular concern as most medications for dementia are cholinergic agents, whose effects can be antagonized by anticholinergics[22]. Indeed, previous studies have shown that up to one third of individuals taking cholinergic agents are also prescribed drugs with anticholinergic effects[23, 24]. As anticholinergics were the most prevalent class of PIMs in our population, particular care should be taken in their prescription to avoid potential adverse effects and interactions.

Although cognitive status appeared to be associated with both PIM use and increased anticholinergic load, we can not differentiate whether the decline in cognitive function is a cause or consequence of the medications. Some evidence indicates that cognitive impairment can follow rather than precede PIM use. For example, previous longitudinal studies have found an association between anticholinergics and cognitive impairment[8, 25], though findings on benzodiazepines have been mixed[26]. On the other hand, it is also possible that a bidirectional relationship exists between cognitive impairment and PIM use. As cognitive impairment develops in older age, psychiatric comorbidities increase as well. Some PIMs may be prescribed to treat these comorbidities as well as contribute to cognitive impairment, thus leading to a cycle of increasing PIM use and cognitive impairment. Ending this cycle may involve seeking safer alternative medications, or increased caregiver education by healthcare providers. For example, if a PIM is prescribed to treat behaviors considered burdensome but not harmful to the caregiver, it may be prudent to discontinue PIM use rather than subject the patient to adverse effects.

This study includes some limitations that may alter the interpretability and validity of the results. For example, the analysis of PIM use and anticholinergic load showed significant associations with cognitive status, but the effect size was small. However, both PIM use and ACB score showed considerable variability which may have attenuated the mean differences between groups or over time. There may also be confounding by indication, such as by sleep quality or anxiety, which were not measured at baseline. Another limitation is the survivor bias inherent in a population of the oldest old, since women in the final analytic cohort were generally healthier compared to those who did not remain in the study. In addition, the actual duration of PIM use is not certain, because only medications taken within 30 days prior to each visit were recorded. Lastly, since our cohort comprised only female participants, our data may not be generalizable to male populations, as previous studies have consistently reported higher PIM use in elderly women, compared to men[27, 28]. It is unknown why females are subject to higher PIM use, although it may be due to women more frequently reporting medical complaints and making more healthcare visits[29]. Additionally, the cognitive effects of anticholinergic use may be gender-specific[30].

In a population of women 85 years of age and above at follow-up, with over 40% having either dementia or MCI, approximately one-quarter reported to be taking at least one PIM. In some cases, after considering individual circumstances, the risk-benefit ratio may merit the use of PIMs as an appropriate an effective treatment. However, there may also be situations when a PIM is not effective, or when viable alternatives exist. Whether or not PIM use leads to long-term cognitive consequences, the short-term adverse effects of these medications are well-established. Therefore, these findings underscore the necessity to limit PIM use in older populations and seek available alternatives when possible. In order to reduce the use of inappropriate medications among the elderly, future guidelines should increase awareness and implementation of PIM criteria in the management and prescription of medications in older populations. These findings also highlight the need for future studies to determine if the observed trajectories of PIM use translate into an association between PIMs and incident cognitive impairment and if cessation of PIM use can result in long-term improvements in cognitive function.

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The sponsors had no role in the study design, methods, subject recruitment, data collection, analysis, and preparation of the manuscript.

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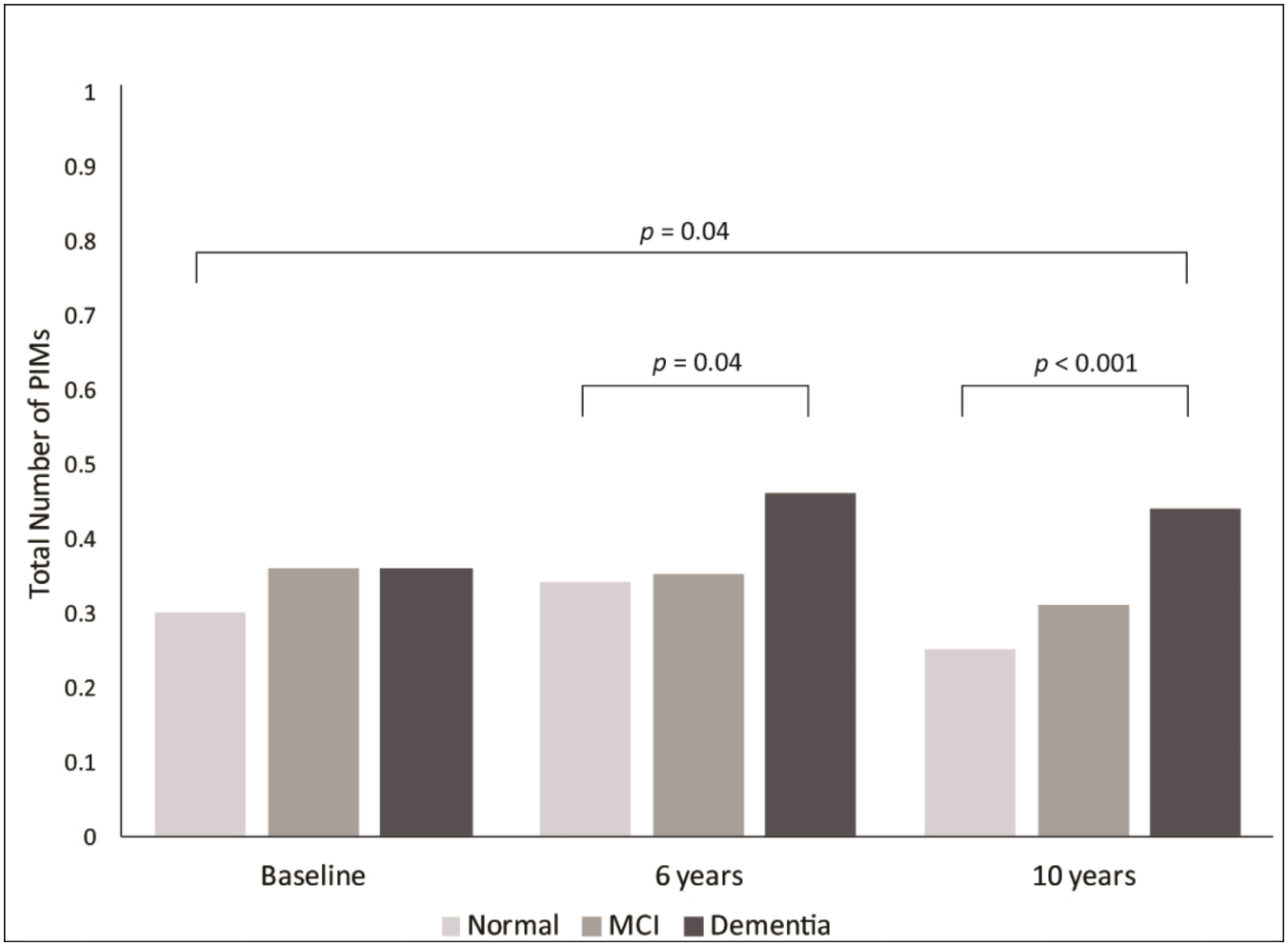

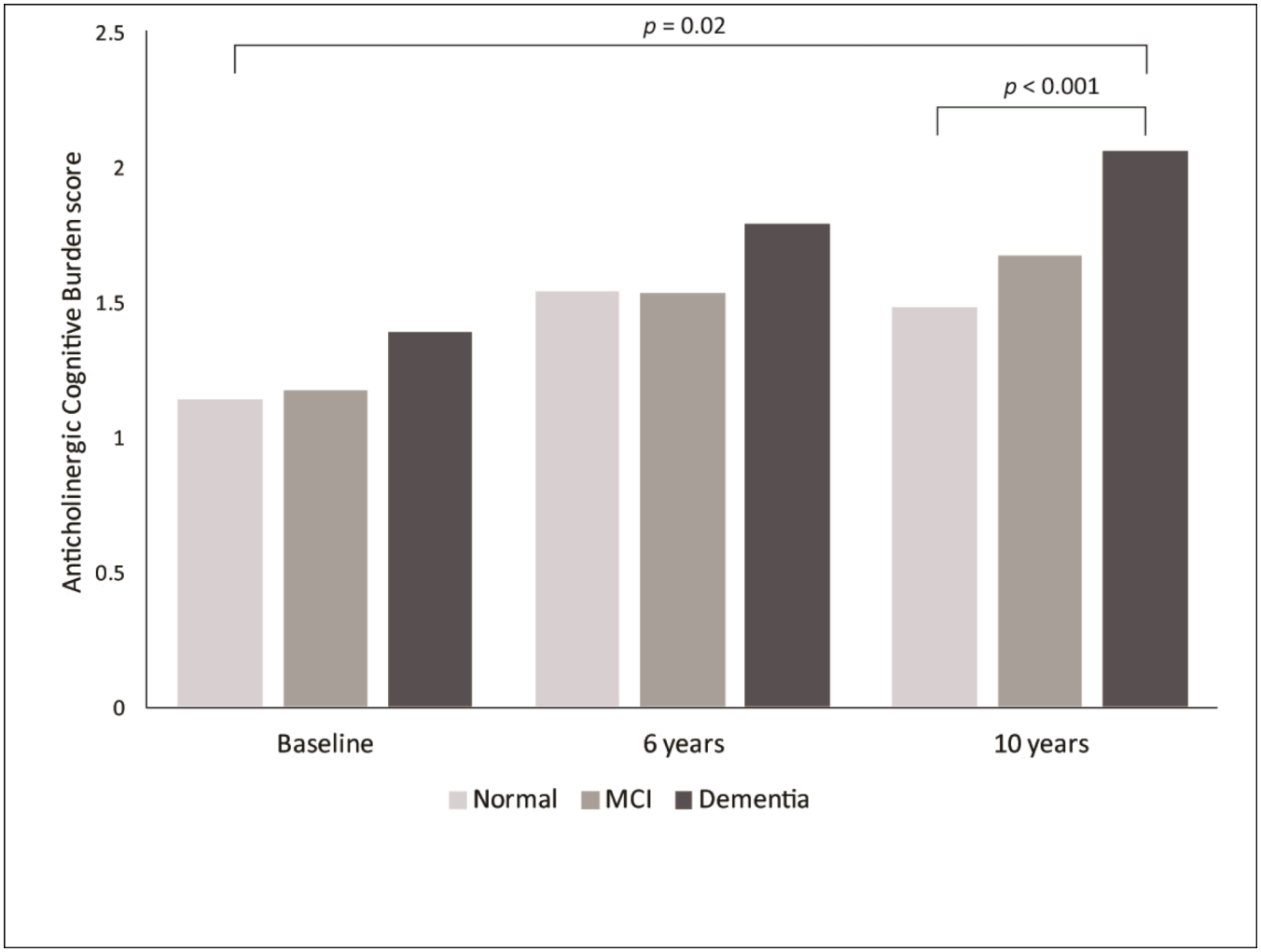

Figure 1.
These column graphs show unadjusted trajectories of mean PIM use and ACB score, by cognitive status. The *p* values within time points indicate significant differences between groups. The *p* values across all time points indicate significantly different rates of change over 10 years between groups.
Abbreviations: MCI = mild cognitive impairment

Table 1

Participant Characteristics at Baseline and 10-year follow-up, by PIM Use (n=1,484)

Characteristic	Baseline		10-year follow-up	
	PIM users (n=358)	non-users (n=1,115)	PIM users (n=354)	non-users (n=1,130)
Age (mean ± SD)	78.0 ± 3.1	78.0 ± 3.2	87.8 ± 3.2	87.4 ± 3.2
Caucasian (n, %)	317 (88.6%)	987 (88.5%)	323 (91.8%)[a]	988 (87.6%)[a]
Education (years, mean ± SD)	12.9 ± 2.7	12.8 ± 2.4	12.6 ± 2.4[a]	12.9 ± 2.5[a]
BMI (mean ± SD)	27.7 ± 4.8	27.5 ± 4.6	26.1 ± 4.0	26.2 ± 3.9
Smoking history (ever, n, %)	131 (36.7%)	361 (32.5%)	124 (35.2%)	372 (33.0%)
Takes walks for exercise (n, %)	156 (43.6%)	525 (47.1%)	135 (39.5%)	469 (42.4%)
Cancer (n, %)	88 (24.7%)	234 (21.3%)	80 (21.5%)	225 (22.4%)
COPD (n, %)	71 (19.9%)[c]	122 (11.0%)[c]	56 (14.9%)[b]	98 (9.7%)[b]
Hypertension (n, %)	184 (51.5%)	527 (47.4%)	236 (67.2%)	743 (65.9%)
Myocardial infarction (n, %)	34 (9.5%)[a]	56 (5.1%)[b]	72 (20.5%)[a]	170 (15.1%)[a]
Osteoarthritis (n, %)	146 (40.8%)[c]	332 (30.0%)[c]	170 (48.4%)[a]	472 (41.8%)[a]
Pittsburgh Sleep Quality Index (n, %)[d]	n/a	n/a	7.5 ± 3.9[c]	6.4 ± 3.7[c]
Stroke (n, %)	22 (7.0%)	49 (5.0%)	51 (14.5%)	141 (12.5%)
Type II diabetes (n, %)	20 (5.6%)	77 (7.0%)	46 (13.6%)	172 (15.1%)
Urinary incontinence (n, %)	n/a	n/a	204 (58.6%)[a]	582 (51.9%)[a]
Geriatric Depression Scale (mean ± SD)[d]	2.0 ± 2.1[c]	1.5 ± 2.1[c]	3.0 ± 2.5[c]	2.4 ± 2.3[c]
Goldberg Anxiety Scale (mean ± SD)[d]	n/a	n/a	2.4 ± 2.6[c]	1.9 ± 2.4[c]
MMSE (mean ± SD)[d]	28.7 ± 1.5	28.6 ± 1.6	26.3 ± 3.3[c]	26.8 ± 3.0[c]

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; MMSE = mini-mental state examination;

[a] $p < 0.05$;

[b] $p < 0.01$;

[c] $p < 0.001$

[d] Normal ranges: Pittsburgh Sleep Quality Index (0–5); Geriatric Depression Scale (0–5); Goldberg Anxiety Scale (0–4); MMSE (24–30).

Table 2

Unadjusted Mean Number of PIMs and Mean ACB score, by Time Point and Cognitive Status

Time	*Number of PIMs, mean(SE)*				*ACB score, mean(SE)*			
	Dementia (n=260)	**MCI (n=354)**	**Normal (n=870)**	**Unadj. *p*[a]**	**Dementia (n=260)**	**MCI (n=354)**	**Normal (n=870)**	**Unadj. *p*[a]**
Baseline	0.36 (0.04)	0.36 (0.03)	0.30 (0.02)	0.21	1.39 (0.11)	1.17 (0.09)	1.14 (0.06)	0.15
6 Years	0.46 (0.04)	0.35 (0.04)	0.34 (0.02)	0.04	1.79 (0.11)	1.53 (0.10)	1.54 (0.06)	0.15
10 Years	0.44 (0.04)	0.31 (0.03)	0.25 (0.02)	<0.001	2.06 (0.10)	1.67 (0.09)	1.48 (0.06)	<0.001
10-yr change	0.08 (0.05)	−0.02 (0.04)	−0.05 (0.02)	0.04	0.67 (0.13)	0.50 (0.11)	0.34 (0.07)	0.02

[a]F-test of group effect