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RESEARCH ARTICLE

Gastric acid suppressants and cognitive decline in people with or without cognitive impairment

Che-Yuan Wu[1,2] | Lisa Y. Xiong[1,2] | Michael Ouk[2] | Jennifer S. Rabin[2,3,4,5] | Nathan Herrmann[6,7] | Krista L. Lanctôt[1,2,7,8] | Moira K. Kapral[9,10,11] | Marcus Law[12,13] | Hugo Cogo-Moreira[2,14] | Jodi D. Edwards[15,16,17] | Walter Swardfager[1,2,8,18]

[1] Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada

[2] Sandra Black Centre for Brain Resilience and Recovery, Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, Ontario, Canada

[3] Harquail Centre for Neuromodulation, Sunnybrook Research Institute, Toronto, Ontario, Canada

[4] Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

[5] Rehabilitation Sciences Institute, University of Toronto, Toronto, Ontario, Canada

[6] Department of Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

[7] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

[8] KITE University Health Network Toronto Rehabilitation Institute, Toronto, Ontario, Canada

[9] ICES, Toronto, Ontario, Canada

[10] Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada

[11] Division of General Internal Medicine, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[12] University Health Network Toronto Rehabilitation Institute, Toronto, Ontario, Canada

[13] Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada

[14] Faculty of Education, ICT, and Learning, Østfold University College, Halden, Norway

[15] University of Ottawa Heart Institute, University of Ottawa, Ottawa, Ontario, Canada

[16] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

[17] ICES, Ottawa, Ontario, Canada

[18] Canadian Partnership for Stroke Recovery, Sunnybrook Research Institute, Toronto, Ontario, Canada

Correspondence
Walter Swardfager, Department of Pharmacology and Toxicology, University of Toronto, 1 King's College Circle, Toronto, Ontario, M5S 1A8, Canada.
Email: w.swardfager@utoronto.ca

Abstract

Introduction: Studies suggest associations between proton pump inhibitors (PPIs) and dementia risk; however, many neither considered histamine-2 receptor antagonists (H2RAs) nor baseline cognitive status.

Methods: Participants (National Alzheimer's Coordinating Center Database; 2005–2021) using a PPI or H2RA were compared. Covariate-adjusted Cox regression was used to estimate hazard ratios (HR) for progression from normal cognition to mild cognitive impairment (MCI), and from MCI to dementia over 5 years. In a propensity-score–matched subsample of mild–moderate Alzheimer's disease (AD),

mixed-effects negative binomial regression was used to estimate decline in delayed recall memory.

Results: Compared to PPI, H2RA use was associated with earlier progression from MCI to dementia (HR = 1.40 [1.09–1.81]; *n* = 1701), and with faster memory decline in AD over time (rate ratio = 0.76 [0.64–0.92]; *n* = 628), but not with progression from normal cognition to MCI (HR = 0.94 [0.71–1.24]; *n* = 2784).

Discussion: Compared to PPIs, H2RAs were associated with cognitive decline, specifically among people with pre-existing cognitive impairment.

KEYWORDS

Alzheimer's disease, cognition, dementia, gastric acid suppressant, histamine-2 receptor antagonist, memory, mild cognitive impairment, proton pump inhibitor

1 | INTRODUCTION

Proton pump inhibitors (PPIs) are gastric acid suppressants and one of the most commonly used medications worldwide.[1] Several observational studies have suggested that PPI use is associated with a higher risk of dementia compared to no use;[2–6] however, many of those studies did not consider the use of histamine-2 receptor antagonists (H2RAs), the other class of acid suppressants used for similar indications.[3–11] Thus, it is unclear whether the previous estimates of dementia risk are due to the drug indication or to the drug itself. Furthermore, increasing evidence suggests that use of H2RAs is associated with greater risks of dementia and cognitive decline compared to no use,[12–15] although those findings have been inconsistent.[16–23] Clinically, physicians or patients may be confronted with choosing either a PPI or an H2RA when potent gastric acid suppression is necessary; therefore, it is important to determine whether one class is associated with a slower rate of cognitive decline compared to the other. Because few studies have specifically compared PPI versus H2RA monotherapy, with mixed evidence,[14,24,25] the present study investigates whether there is a difference in cognitive decline between H2RA versus PPI monotherapy users.

The majority of studies examining acid suppressant use and cognitive decline have focused on incident dementia.[2–8,11–14,17,24,25] Few studies have examined the association between cognitive decline and PPI versus H2RA use in people with pre-existing cognitive impairment who may be particularly vulnerable to their adverse (e.g., anticholinergic) effects.[26,27] Therefore, the present study examines longitudinal associations between H2RA versus PPI use and cognitive decline in a large sample stratified by baseline cognitive status, to determine specifically whether the evidence suggests that a particular acid suppressant may be more detrimental to cognition and whether the association may differ by baseline cognitive status. We hypothesized that H2RA use would be associated with greater cognitive decline over time compared to PPI use, specifically in people with cognitive impairment. Because acid suppressants are some of the most commonly used drugs, evidence of differential risks between the classes would help to optimize pharmacotherapy for many older people requiring an acid suppressant, with potential for broad public health implications.

2 | METHODS

2.1 | Data source

The National Alzheimer's Coordinating Center (NACC) was established in 1999, and is comprised of case-series data from approximately 42 Alzheimer's Disease Research Centers (ADRCs) funded by National Institute on Aging (NIA) across the United States. Data are collected in a standardized manner from different ADRCs to form the Uniform Data Set (UDS), as described previously.[28,29] The UDS was implemented in September 2005, and the dataset is still expanding. The ADRCs enroll participants through referral by clinicians, family members, or patients themselves, and through active recruitment from community organizations. Written informed consent was obtained from all participants and co-participants (usually a close friend or family member). Participants were followed up for UDS visits approximately annually, and the UDS data collection forms were completed by clinicians.

2.2 | Sample selection

Participants using an H2RA or PPI were selected. People with cancer or on chemotherapy were excluded from the study. Analyses were performed separately in people with clinically diagnosed mild–moderate Alzheimer's disease (AD), mild cognitive impairment (MCI), and normal cognition. Prevailing clinical diagnostic criteria and the Clinical Dementia Rating (CDR® Dementia Staging Instrument) were used to classify participants into each study group.[30]

Participants who had a global CDR score of 1 or 2 and met NIA and Alzheimer's Association (NIA-AA) or National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease

and Related Disorders Association criteria were included in the group of clinically diagnosed mild–moderate AD.[31,32] Participants who had a global CDR score of 0.5 and met the Petersen's criteria were included in the MCI group.[33] Normal cognitive status was based on clinician judgment, and all participants included in the normal cognition group had a global CDR score of 0. Cognitively normal participants on a drug for dementia (i.e., cholinesterase inhibitors or memantine) at baseline were excluded. Within each study group, CDR Sum of Boxes (CDR-SOB) was further used to mitigate potential misclassification bias. Cognitively normal individuals who had CDR-SOB > 0.5 at baseline, those with MCI who had CDR-SOB > 4 at baseline, and those with mild–moderate AD who had CDR-SOB > 15 at baseline were excluded.

2.3 | Drug exposure

Medication use at each visit was collected using a structured medication inventory. Participants or co-participants were asked to bring to the study visit or report medications used currently or within the past 2 weeks, and the medication form was completed by trained ADRC staff physicians. All prescription medications were required to be reported, but it was optional to report over-the-counter drugs.

Participants who reported using an H2RA or PPI at the baseline of the analysis were classified as an H2RA or PPI user, respectively, but those using both an H2RA and a PPI at the baseline of the analysis were excluded. Data after a switch from an H2RA to a PPI (and vice versa) were censored to avoid risk factor misattribution. Data beyond discontinued use of H2RAs or PPIs were not censored, as there might be carry-over effects of drug exposure or a lag in cognitive decline.[24]

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors evaluated current clinical studies investigating cognitive decline in people using proton pump inhibitors (PPIs) and/or histamine-2 receptor antagonists (H2RAs). There was conflicting evidence, and most prior studies did not directly compare H2RAs with PPIs or consider baseline cognitive status.
2. **Interpretation**: H2RA users with mild cognitive impairment (MCI) at baseline showed earlier progression to dementia over 5 years compared to PPI users. H2RA use was associated with faster memory decline in mild–moderate Alzheimer's disease (AD). No increased risk of dementia or associations with cognitive performance were found in cognitively normal people.
3. **Future Directions**: Both classes are generally indicated for short-term use, and may have adverse effects. Further studies might compare these risks at different exposure durations and doses between specific drugs within the classes. Assays comparing anti-cholinergic potential between the two classes may be useful.

2.4 | Cognitive outcomes

In normal cognition, the primary outcome was time to MCI or all-cause dementia (if dementia was diagnosed without a preceding MCI diagnosis). In MCI, the primary outcome was time to all-cause dementia. Identification of MCI or dementia was made by clinician judgment at every UDS visit. MCI diagnosis was based on Petersen's criteria.[33] Participants were considered to meet dementia criteria when they exhibited symptoms that interfered with daily functioning, exhibited functional decline, had low performance on cognitive assessments, showed impairment in at least one cognitive domain, and cognitive decline could not be explained by a major psychiatric disorder or delirium, and/or when they fulfilled other established clinical criteria for dementia, as described in the NACC database.[30,31]

To explore a sensitive and specific cognitive domain related to AD, delayed recall memory was examined in people with normal cognition, MCI, and mild–moderate AD. Delayed recall memory performance was assessed using the Wechsler Memory Scale Revised—Logical Memory test IIA (score range from 0 to 25; better scores indicate better performance in episodic memory).[34]

A follow-up window over 5 years from baseline plus a 6-month censoring interval (i.e., 5.5 years to capture most 5-year visits) was applied to all the outcomes to infer the associations between baseline drug use and cognition with more confidence while also considering the possible carry-over effects of drugs.

2.5 | Statistical analysis

All analyses were conducted using R 4.0.5,[35] and the figures were created using the graphics or ggplot2 packages.[35,36]

Cox proportional hazards regression models were used to assess whether baseline use of H2RA versus PPI was associated with differential conversion from normal cognition to cognitive impairment due to MCI or dementia, and differential conversion from MCI to dementia over 5 years (survival package).[37] To address potential confounders, the hazard ratios (HRs) were adjusted for baseline covariates, including age, sex, CDR-SOB as a general functional measure for cognitive impairment, ethnicity (White vs. not White), years of education, body mass index, apolipoprotein E (*APOE*) $\varepsilon 4$ genotype, vitamin B_{12} deficiency, diabetes, hypertension, hyperlipidemia, depression, cardiovascular disease, history of stroke or transient ischemic attack (TIA), polypharmacy (> 7 drugs reported), active or recent smoking status, alcohol abuse, and reported use of antacids, multivitamins, anti-inflammatory agents, anti-coagulants, and medications for dementia. The proportional hazards assumption was inspected using scaled Schoenfeld residuals. An independent variable was considered to violate the assumption when the scaled Schoenfeld residuals did not fit a straight horizontal line over time.

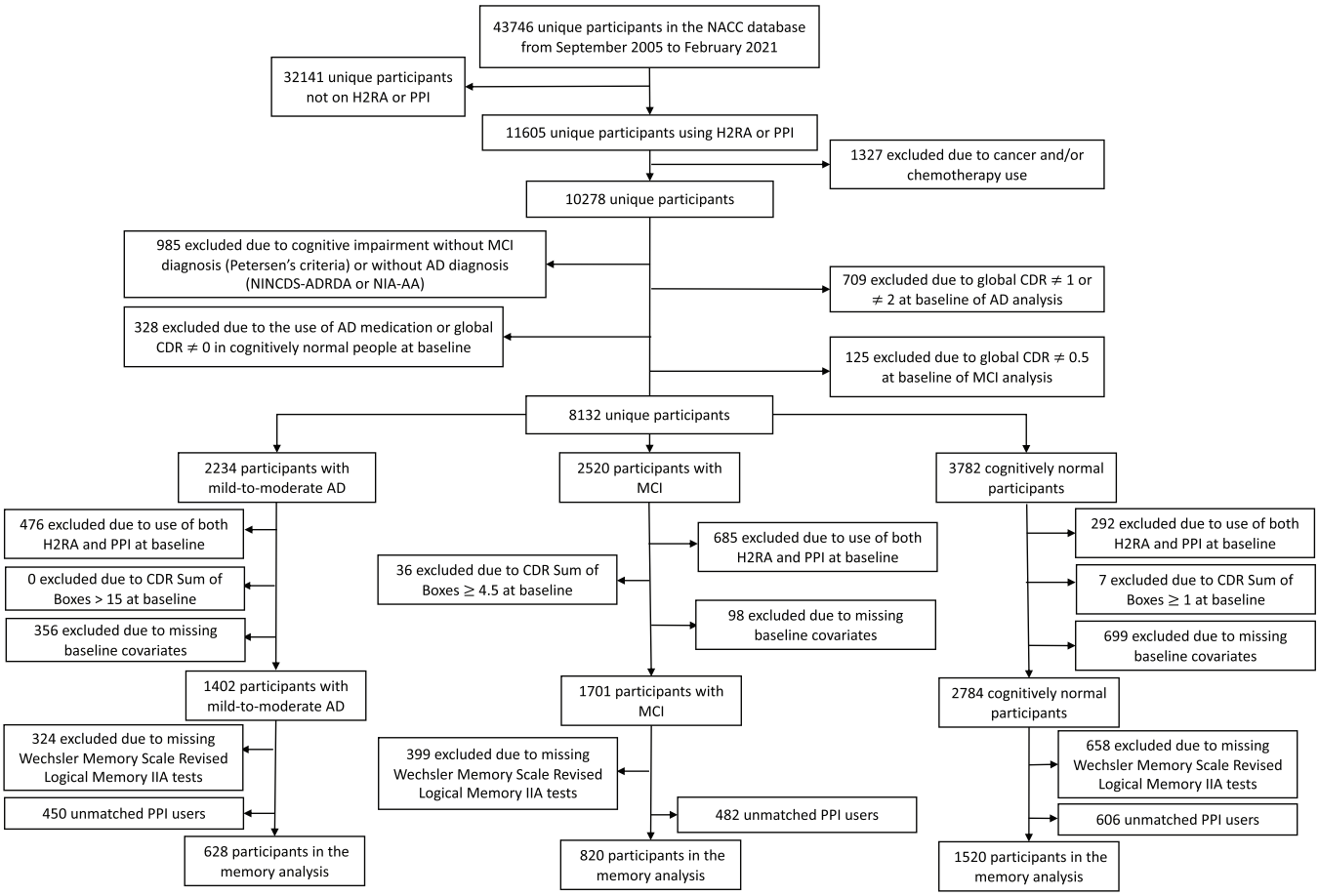

FIGURE 1 Sample selection. The diagram showed how participants in each study group were selected from the National Alzheimer's Coordinating Center (NACC) database. AD, Alzheimer's disease; CDR, Clinical Dementia Rating; H2RA, histamine-2 receptor antagonist; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging–Alzheimer's Association; NINCDS-ARDRA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; PPI, proton pump inhibitor

For analyses of memory performance, participants with available baseline covariates and delayed recall memory scores at any visit were included. Within normal controls, MCI, and mild–moderate AD groups, H2RA users were matched to PPI users by propensity score (MatchIt package) using the greedy nearest neighbor matching method with a ratio of 1:3.[38] The abovementioned baseline covariates were included in the propensity score calculation as potential confounders, and a standardized difference < 0.1 was considered balanced. As the delayed recall memory score is a count variable, a random-intercept mixed-effects negative binomial regression model controlling for concurrent use of dementia medication at each visit was used to assess baseline use of an H2RA versus PPI in rates of change in delayed recall memory over 5 years (lme4 package).[39] A mixed-effects Poisson regression model was chosen when the data could not fit a negative binomial regression owing to no overdispersion. The longitudinal association was assessed by a drug × time interaction term in the model, and the effect size was expressed as a rate ratio (RR), indicating the fold-change in score over time. An RR smaller than 1 indicated faster decline in the non-reference level.

3 | RESULTS

3.1 | Participant characteristics

Of 43,746 participants from September 2005 to February 2021, a total of 11,605 participants were identified to have used an H2RA and/or PPI. Details of the selection process are shown in Figure 1. A total of 1701 people with MCI and 2784 people with normal cognition met the inclusion criteria and were included in the analyses for the progression to cognitive impairment or dementia. Baseline characteristics of H2RA and PPI users with normal cognition or MCI that were included in the analyses are shown in Table 1. The baseline characteristics of propensity score–matched samples included in the memory analyses are shown in Table 2. The memory analyses consisted of 628, 820, and 1520 people with mild–moderate AD, MCI, and normal cognition, respectively.

Among participants included in all analyses, there were no users of anticholinergic agents for ulcer treatment (pirenzepine, propantheline, or oxyphenonium).

TABLE 1 Baseline subject characteristics for normal cognition and MCI

	Normal cognition		Mild cognitive impairment	
	H2RA users ($n = 547$)	PPI users ($n = 2237$)	H2RA users ($n = 288$)	PPI users ($n = 1413$)
Age	73.11 (9.69)	73 (9.35)	76.22 (9.61)	75.7 (9.11)
Female	67% (364)	66% (1477)	55% (158)	52% (734)
White	81% (445)	83% (1846)	78% (226)	83% (1173)
Years of education	15.45 (3.01)	15.53 (3.01)	14.91 (3.5)	15.06 (3.39)
Body mass index	27.91 (5.40)	28.54 (5.45)	27.95 (5.78)	27.71 (5.12)
APOE"4 carriers	30% (166)	28% (632)	39% (112)	40% (559)
Vitamin B12 deficiency	4% (24)	5% (114)	10% (28)	8% (108)
Diabetes	16% (85)	16% (350)	19% (56)	20% (281)
Hypertension	56% (307)	62% (1384)	64% (183)	65% (920)
Hyperlipidemia	58% (319)	61% (1369)	58% (167)	67% (944)
Depression	10% (57)	12% (265)	25% (73)	27% (375)
Cardiovascular disease	25% (137)	24% (532)	28% (80)	30% (427)
Stroke or TIA history	11% (58)	8% (169)	14% (39)	15% (211)
Polypharmacy (> 7 drugs)	52% (287)	52% (1158)	56% (161)	60% (844)
Antacid use	13% (71)	9% (204)	7% (20)	10% (138)
Multivitamin use	42% (230)	42% (934)	33% (94)	40% (562)
Anti-inflammatory use	53% (290)	50% (1109)	49% (142)	52% (728)
AD medication	–	–	22% (62)	23% (322)
Alcohol abuse	4% (20)	4% (90)	6% (17)	7% (95)
Recent or active smoking	43% (234)	47% (1051)	49% (141)	46% (652)
Anti-coagulant use	47% (259)	44% (974)	52% (150)	51% (721)
CDR SOB				
CDR SOB = 0.5 versus. = 0	5% (25)	4% (79)	–	–
CDR SOB	–	–	1.42 (0.92)	1.32 (0.89)
H2RA				
Cimetidine	3% (15)	–	2% (5)	–
Famotidine	30% (162)	–	35% (100)	–
Nizatidine	1% (7)	–	<1% (1)	–
Ranitidine	67% (364)	–	64% (183)	–
PPI				
Dexlansoprazole	–	1% (23)	–	1% (15)
Esomeprazole	–	15% (330)	–	15% (214)
Lansoprazole	–	8% (179)	–	9% (121)
Pantoprazole	–	15% (328)	–	16% (225)
Omeprazole	–	59% (1322)	–	56% (795)
Rabeprazole	–	4% (81)	–	4% (52)

Note: Categorical variables were reported in proportion (frequency), and continuous variables were reported in mean (standard deviation).
Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; CDR SOB, Clinical Dementia Rating Sum of Boxes; H2RA, histamine-2 receptor antagonist; MCI, mild cognitive impairment; PPI, proton pump inhibitor; TIA, transient ischemic attack.

TABLE 2 Baseline subject characteristics (exploratory analyses for memory)

	Normal cognition				Mild cognitive impairment				Mild-to-moderate AD			
	H2RA users ($n = 380$)	Matched PPI users ($n = 1140$)	*P*-value	Std. Dif.	H2RA users ($n = 205$)	Matched PPI users ($n = 615$)	*P*-value	Std. Dif.	H2RA users ($n = 157$)	Matched PPI users ($n = 471$)	*P*-value	Std. Dif.
Age	74.64 (9.57)	74.22 (9.31)	.440	0.045	76.78 (9.54)	76.66 (9.04)	.869	0.013	77.27 (9.6)	77.62 (8.77)	.672	0.038
Female	65% (248)	65% (738)	.852	0.011	54% (110)	56% (346)	.516	0.052	57% (89)	57% (268)	.963	0.004
Whites	83% (314)	83% (942)	>.999	0.000	75% (154)	75% (464)	.925	0.008	77% (121)	80% (376)	.513	0.057
Years of education	15.19 (3.18)	15.23 (3.1)	.835	0.012	14.54 (3.77)	14.56 (3.37)	.940	0.006	13.54 (4.7)	13.78 (3.7)	.919	0.009
Body mass index	27.84 (5.35)	28.01 (5.41)	.588	0.032	28.08 (5.72)	28.08 (5.65)	.992	0.001	26.94 (4.89)	26.99 (5.08)	.746	0.030
APOE"4 carriers	28% (108)	28% (324)	>.999	0.000	39% (80)	41% (254)	.566	0.046	57% (89)	55% (257)	.606	0.047
Vitamin B12 deficiency	5% (20)	5% (58)	.893	0.008	10% (20)	8% (51)	.519	0.051	8% (13)	9% (43)	.668	0.040
Diabetes	16% (60)	15% (166)	.560	0.034	20% (42)	20% (121)	.801	0.02	22% (34)	20% (93)	.712	0.034
Hypertension	62% (236)	62% (704)	.903	0.007	68% (139)	67% (412)	.830	0.017	73% (115)	74% (349)	.834	0.019
Hyperlipidemia	62% (235)	62% (708)	.927	0.005	60% (122)	60% (371)	.837	0.017	63% (99)	64% (300)	.886	0.013
Depression	10% (37)	9% (102)	.644	0.027	26% (54)	26% (160)	.927	0.007	34% (54)	34% (161)	.961	0.004
Cardiovascular disease	27% (103)	26% (296)	.662	0.026	32% (65)	31% (193)	.931	0.007	24% (37)	25% (120)	.915	0.01
Stroke or TIA history	13% (51)	12% (141)	.593	0.031	17% (34)	16% (98)	.826	0.018	14% (22)	15% (71)	.713	0.034
Polypharmacy (> 7 drugs)	50% (189)	49% (559)	.813	0.014	55% (112)	55% (336)	>.999	0.000	63% (99)	66% (313)	.643	0.043
Antacid use	12% (44)	11% (129)	.889	0.008	8% (17)	9% (58)	.624	0.04	10% (16)	11% (53)	.461	0.067
Multivitamin use	40% (151)	40% (452)	.976	0.002	30% (61)	33% (204)	.365	0.074	36% (56)	38% (177)	.632	0.044
Anti-inflammatory use	52% (197)	53% (603)	.722	0.021	49% (101)	50% (307)	.872	0.013	48% (76)	50% (236)	.746	0.03
Dementia medication	–	–	–	–	20% (42)	22% (137)	.591	0.044	71% (111)	71% (335)	.692	0.036
Alcohol abuse	4% (14)	4% (44)	.877	0.009	7% (14)	8% (49)	.596	0.043	6% (10)	6% (26)	.674	0.039
Recent or active smoking	47% (177)	47% (534)	.929	0.005	51% (105)	53% (325)	.686	0.033	40% (63)	42% (198)	.438	0.071
Anti-coagulant use	48% (184)	49% (553)	.976	0.002	54% (111)	53% (329)	.872	0.013	49% (77)	51% (241)	.925	0.009

(Continues)

TABLE 2 (Continued)

	Normal cognition				Mild cognitive impairment				Mild-to-moderate AD			
	H2RA users ($n = 380$)	Matched PPI users ($n = 1140$)	*P*-value	Std. Dif.	H2RA users ($n = 205$)	Matched PPI users ($n = 615$)	*P*-value	Std. Dif.	H2RA users ($n = 157$)	Matched PPI users ($n = 471$)	*P*-value	Std. Dif.
CDR SOB												
CDR SOB = 0.5 versus = 0	6% (22)	5% (56)	.502	0.039	–	–	–		–	–	–	
CDR SOB	–	–	–	–	1.52 (0.96)	1.51 (0.97)	.901	0.01	7.02 (2.69)	6.99 (2.68)	.645	0.042
H2RA												
Cimetidine	4% (14)	–	–	–	2% (5)	–	–	–	3% (4)	–	–	–
Famotidine	28% (105)	–	–	–	35% (71)	–	–	–	35% (55)	–	–	–
Nizatidine	2% (7)	–	–	–	0% (0)	–	–	–	2% (3)	–	–	–
Ranitidine	67% (255)	–	–	–	63% (130)	–	–	–	61% (95)	–	–	–
PPI												
Dexlansoprazole	–	1% (10)	–	–	–	1% (5)	–	–	–	0% (0)	–	–
Esomeprazole	–	15% (174)	–	–	–	16% (101)	–	–	–	18% (85)	–	–
Lansoprazole	–	10% (109)	–	–	–	11% (68)	–	–	–	7% (33)	–	–
Pantoprazole	–	11% (127)	–	–	–	13% (80)	–	–	–	16% (74)	–	–
Omeprazole	–	59% (670)	–	–	–	56% (344)	–	–	–	56% (265)	–	–
Rabeprazole	–	5% (54)	–	–	–	3% (21)	–	–	–	3% (15)	–	–

Note: Categorical variables were reported in proportion (frequency), and continuous variables were reported in mean (standard deviation). Pooled *t*-test and Chi-square test were used to test between-group difference for continuous and categorical variables, respectively.

Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; CDR SOB, Clinical Dementia Rating Sum of Boxes; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; TIA, transient ischemic attack; Std. Dif., standardized difference.

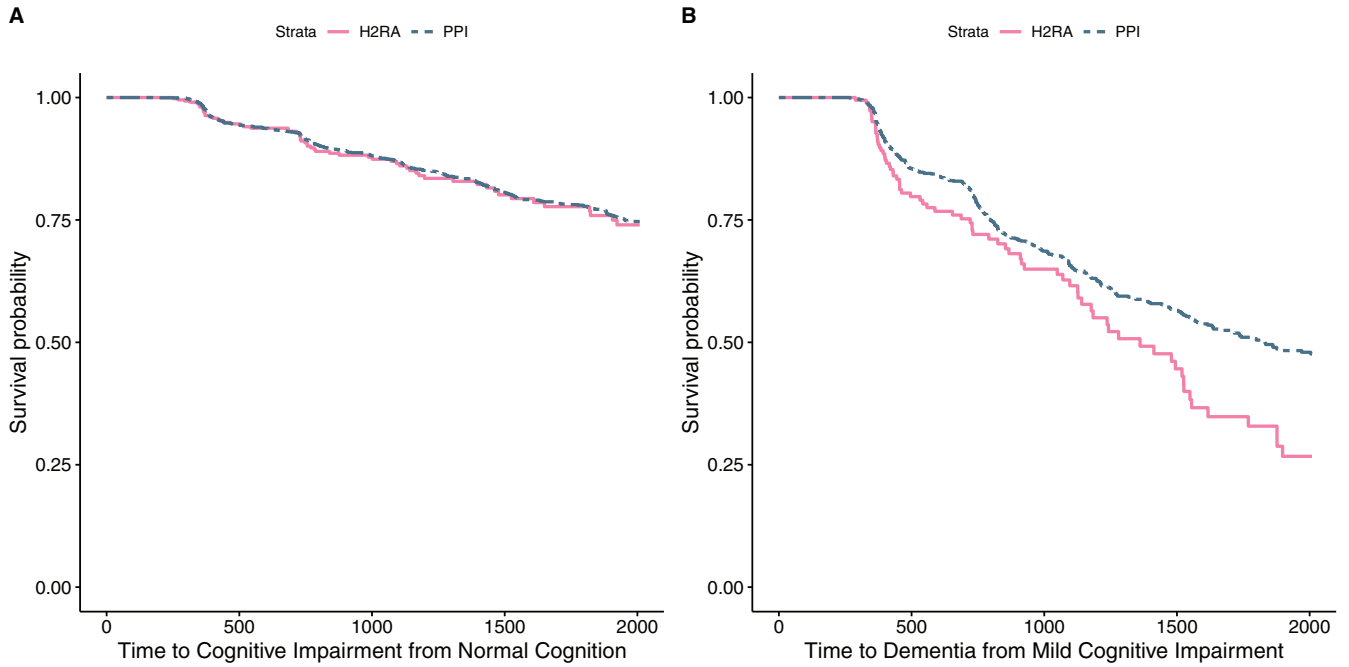

FIGURE 2 Kaplan-Meier curves of (A) conversion from normal cognition to cognitive impairment (MCI or dementia) and (B) progression from MCI to dementia, between H2RA and PPI users over 5 years. The use of H2RAs was associated with earlier MCI-to-dementia progression over 5 years (adjusted HR [95% CI] = 1.402 [1.085–1.811], $P = .010$, Ref: PPI), whereas no association with the risk for cognitive impairment (MCI or dementia) was seen in people with normal cognition (adjusted HR [95% CI] = 0.937 [0.709–1.239], $P = .648$, Ref: PPI). CI, confidence interval; H2RA, histamine-2 receptor antagonist; HR, hazard ratio; MCI, mild cognitive impairment; PPI, proton pump inhibitor; Ref, reference level

3.2 | Progression to cognitive impairment or dementia in H2RA versus PPI users with normal cognition or MCI

Over 2.70 ± 2.06 years of follow-up, cognitively normal H2RA ($n = 547$, events = 62; 2.27 ± 1.88 years of follow-up; 0.050 events/person-year) and PPI users ($n = 2237$, events = 312; 2.80 ± 2.09 years of follow-up; 0.050 events/person-year) did not differ in their 5-year risk for cognitive impairment due to MCI or dementia (HR [95% confidence interval (CI)] = 0.937 [0.709–1.239], $P = .648$). In the MCI group, over 1.90 ± 1.76 years of follow-up, H2RA use ($n = 288$, events = 75; 1.48 ± 1.58 years of follow-up; 0.175 events/person-year) was associated with earlier progression from MCI to dementia within 5 years (HR [95% CI] = 1.402 [1.085–1.811], $P = .010$), compared to PPI use ($n = 1413$, events = 355; 1.99 ± 1.79 years of follow-up; 0.126 events/person-year). The Kaplan-Meier curves are shown in Figure 2. The exposure variable in the model for MCI-dementia conversion within 5 years did not violate the proportional hazards assumption (Figure S1 in supporting information).

3.3 | Memory decline in H2RA versus PPI users

In mild–moderate AD (mean 1.71 ± 1.73 years of follow-up), H2RA use ($n = 157$; 1.53 ± 1.72 years of follow-up) was associated with faster memory decline (RR [95% CI] = 0.783 [0.671, 0.915], $P = .002$) than PPI use ($n = 471$; 1.77 ± 1.73 years of follow-up) in a mixed-effects negative binomial model. No associations with memory decline were found in MCI, or normal cognition in mixed-effects Poisson models (Figure 3).

3.4 | Post hoc analyses

In post hoc analyses including all available data regardless of time from baseline (Figure S2 and S3 in supporting information), the results were similar for all outcomes. There remained a trend indicating that H2RA users exhibited earlier MCI-to-dementia progression, but the association did not reach significance (HR [95% CI] = 1.285 [0.997–1.656], $P = .053$; Figure S2); however, confidence in that estimate may be reduced as the proportional hazards assumption was potentially violated after 5.5 years for the exposure variable (Figure S4 in supporting information).

Excluding events within 1 year from the survival analyses did not change our conclusion (cognitively normal: HR [95% CI] = 0.913 [0.671–1.242], $P = .560$, $n = 2733$, events = 232; MCI: HR [95% CI] = 1.384 [1.046–1.832], $P = .023$, $n = 1642$, events = 371).

When 68 participants with MCI were excluded who developed dementia without an AD diagnosis, H2RA use ($n = 275$, events = 62) was associated with earlier progression from MCI to AD over 5 years (HR [95% CI] = 1.376 [1.038–1.824], $P = .027$) than PPI use ($n = 1349$, events = 300).

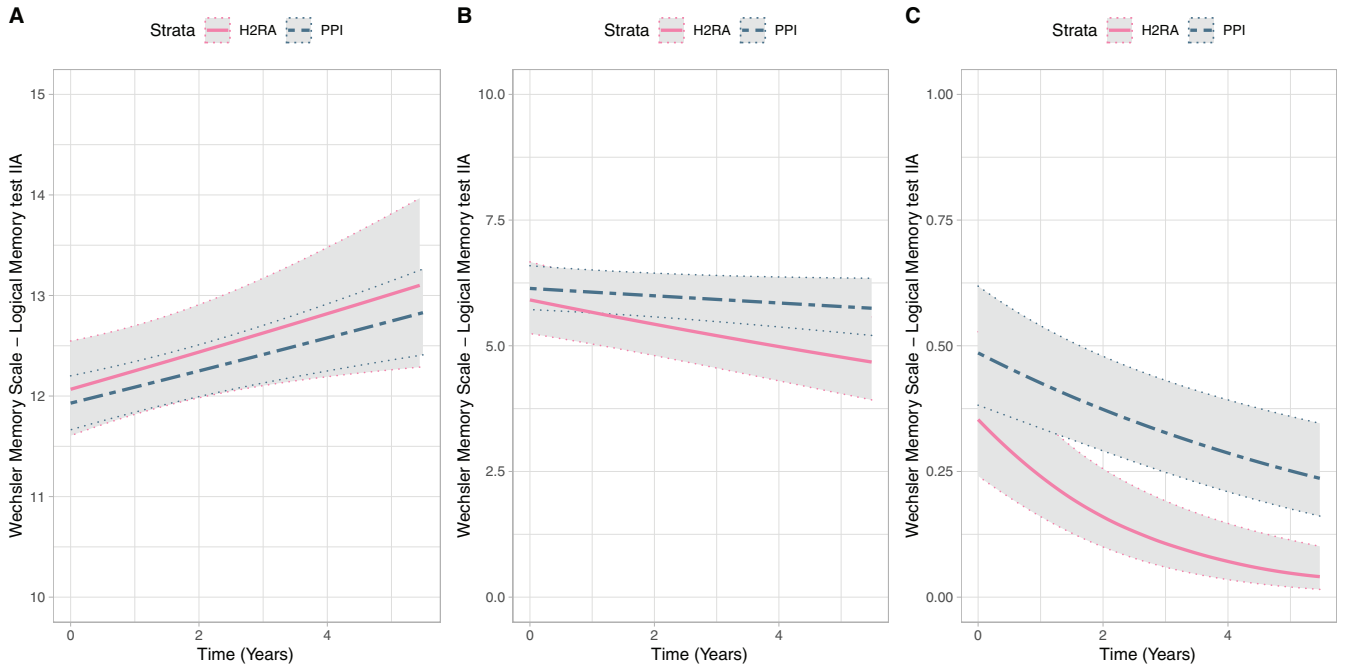

FIGURE 3 Association between delayed recall memory performance over time and the use of H2RAs or PPIs in propensity score matched samples with (A) normal cognition, (B) MCI, and (C) mild–moderate AD over 5 years. Thick lines show the predicted association over time; gray area shows 95% CIs. H2RA use was associated with faster memory decline over time in AD (RR [95% CI] = 0.783 [0.671, 0.915], $P = .002$, Ref: PPI), whereas no longitudinal association was seen in MCI (RR [95% CI] = 0.970 [0.940, 1.001], $P = .056$, Ref: PPI) or normal cognition (RR [95% CI] = 1.002 [0.988, 1.016], $P = .794$, Ref: PPI). AD, Alzheimer's disease; CI, confidence interval; H2RA, histamine-2 receptor antagonist; HR, hazard ratio; MCI, mild cognitive impairment; PPI, proton pump inhibitor; Ref, reference level; RR, rate ratio

To assess how robust the HR is to unmeasured confounding, we calculated an E-value,[40] which is on a risk ratio scale and denotes how strong an unmeasured confounder associated with both the exposure and outcome would need to be to explain away the observed association. The covariate-adjusted HR for MCI-to-dementia progression for H2RAs versus PPIs yielded an E-value of 1.84 (lower CI: 1.31), meaning an unmeasured confounder would require a risk ratio of 1.84 to explain away the observed association (a confounder weaker than 1.31 could not). For context, *APOE* ε4 had an HR of 1.56 (estimated risk ratio: 1.36) in the model. Stronger unmeasured confounders explaining away the association are unlikely because the estimate of this strong risk factor is close to the lower E-value CI.

In a post hoc model comparing antacid (negative control exposure), H2RA, and PPI users ($\chi^2 = 6.41$, DF = 2, $P = .041$) in MCI, H2RA users showed a similar trend toward earlier progression to dementia (HR [95% CI] = 1.258 [0.912–1.737], $P = .162$) compared to antacid monotherapy users ($n = 284$, events = 89), while PPIs versus antacids did not (HR [95% CI] = 0.900 [0.703–1.152], $P = .403$); the HR for PPI versus H2RA users was consistent with the previous model (HR [95% CI] = 1.399 [1.084–1.805], $P = .010$).

4 | DISCUSSION

Among people using H2RA or PPI monotherapy, H2RA use was associated with earlier progression from MCI to dementia in people with MCI, and faster memory decline over 5 years in people with mild–moderate AD. No longitudinal relationships with cognitive decline were seen in people with normal cognition. Directly comparing patients using an H2RA versus a PPI in multiple strata, the results may be relevant to physicians and patients weighing the potential harms associated with the drug when acid suppression is required. Specifically, the evidence would be consistent with individuals with pre-existing cognitive impairment being more vulnerable to the adverse cognitive effects of H2RAs than PPIs.

The present study stratifies people into groups, with and without MCI at baseline, finding that H2RA use was associated with a 40.2% higher dementia risk, specifically for people with MCI. A previous study demonstrated a higher but insignificant risk for dementia (HR [95% CI] = 1.22 [0.85–1.72]) in H2RA users compared to PPI users.[25] Another study showed that both H2RA and PPI monotherapy users had a higher risk of dementia (HR [95% CI] = 1.84 [1.49–2.20] and 1.64 [1.14–1.92], respectively) compared to users of neither.[14] The present results also agree with those of a previous study comparing exposure to an H2RA versus a PPI, in which H2RA use was associated with a higher incidence of dementia within 3 years (HR [95% CI] = 1.45 [1.33–1.45]).[24] Those studies did not stratify samples by the presence of MCI at baseline, which may explain why there is mixed evidence for dementia risk in PPI versus H2RA users. The present results add new evidence that dementia risk was specific to earlier progression among people with pre-existing MCI.

The present findings address further contradictions that have arisen in previous literature. Meta-analyses of dementia risk in PPI users versus non-users suggested high heterogeneity across studies,[3,7,17] and associations between PPI use and dementia risk were not seen among studies that controlled for the use of H2RAs.[13,41–43] Therefore, H2RA exposure may have confounded the PPI risk estimates in several previous studies. In two longitudinal studies,[12,13] H2RA use was associated with higher dementia risk compared to no use, while PPI use was not. Taken with the present results, the evidence *in toto* suggests that H2RAs rather than PPIs might be associated with dementia risk.

H2RA versus PPI use was associated with faster decline in memory performance over time in people with mild–moderate AD, and there was a faster rate of memory decline in H2RA users with MCI, although the latter did not reach significance. A cross-sectional study demonstrated that H2RA rather than PPI use was associated with worse performance in several cognitive domains.[15] A longitudinal analysis showed that neither PPI nor H2RA use was associated with memory decline in cognitively normal people.[23] Those findings are consistent with the present evidence, but we further highlight that H2RAs may be more detrimental than PPIs to certain aspects of cognition, specifically in people with pre-existing cognitive impairment, having marked effects on memory performance among people with clinical AD.

A conflicting study found that PPI users had greater odds of reporting memory impairment compared to H2RA users in the United States Food and Drug Administration (FDA) adverse event reporting system from 2004 to 2018.[21] Two case-control studies reported no association between use of an H2RA and likelihood of dementia.[16,19] Those contradictory results were mainly from cross-sectional or case-control studies, whereas the present study examined cognitive decline prospectively, and it is the first report to show a longitudinal association between faster decline in memory performance and H2RA versus PPI use in people with clinically diagnosed AD.

The biological plausibility of the present findings is supported by a potential dose-response relationship between H2RA use and dementia risk observed in several studies,[14,18] while no study has found a substantial dose-response relationship for PPI use.[8,11,42,44] H2RAs have been suggested to be anticholinergic in vitro,[26] and they are included in the anticholinergic cognitive burden scale.[45] Recently, PPIs were also found to have anticholinergic potential.[27] Anticholinergic burden may explain the association between H2RA use and cognitive decline particularly among those with loss of cholinergic synapses in MCI and AD. Also, PPIs and H2RAs were suggested to have differential effects on gut microbiome,[46] which might be explored as a mediator. As a limitation, data on the microbiome and *H. pylori* infection were not available in the dataset precluding subgroup analyses for different indications.[47]

Both H2RAs and PPIs have been linked to vitamin B_{12} deficiency, which may lead to cognitive decline.[48] In addition, PPIs promoted AD pathology in preclinical studies,[49] and a randomized controlled trial of healthy young volunteers found that PPI use could impair cognition,[50] suggesting that the PPIs are not likely without potential harm. However, clinically when potent acid suppression is necessary, a choice must be made between the classes, which should be informed by clinical evidence comparing the two options. The present findings provide evidence that the PPIs may be less detrimental than H2RAs in the context of cognitive impairment; however, randomized controlled trial data comparing them directly at different doses in specific populations who require acid suppression are lacking.

There were fewer long-term H2RA users than long-term PPI users in the current analysis, suggesting that using only data within 5 years might be more reliable than using data across all available time points when trying to infer effects of the drug exposure. Switching from an H2RA to a PPI was more frequent than vice versa; 50 out of 288 (17%) baseline H2RA users switched to a PPI whereas 86 out of 1413 (6%) PPI users switched to an H2RA within 5 years. Switchers were censored to avoid misattribution of harms. Because this censoring may have been informative, the true harms of H2RAs might have been greater than those estimated; however, associations were still identified.

As another limitation, variables such as prescription versus over-the-counter H2RAs/PPIs, disease severity, ulcer diagnosis, and socioeconomic status were not available, which might introduce residual confounding, as H2RA monotherapy users might represent those with milder gastroesophageal reflux disease symptoms or those with poorer health care access. Nonetheless, analyses with the E-value and negative control exposure implied that the association was likely robust to such unmeasured confounders. Drug exposure prior to entry into the database was not available, and reporting of over-the-counter drugs was optional, which could have introduced some misclassification bias. Dose, duration, and frequency of drug use were not available; thus, cumulative effects and potential dose-response relationships could not be well studied. Also, interval censoring led to loss of information of drug use and cognitive status between visits; however, the identification of MCI or dementia based on prdefined criteria at each visit offered higher confidence in classification of the time of the outcome compared to community samples. Last, the sample size was insufficient to explore differences associated with individual drugs within the classes, risks of specific types of dementia, or associations with cognitive decline in people with cognitive impairment not due to MCI or AD; however, a post hoc analysis suggested that the association was consistent among those who converted specifically to AD dementia.

5 | CONCLUSION

No differential risk for incident clinical cognitive impairment or memory decline was seen between H2RA and PPI use in older people with normal cognition; however, among people with MCI, H2RA users had earlier progression to dementia over 5 years compared to PPI users. Also, H2RA use was associated with faster memory decline in people with mild–moderate AD, but not in people with normal cognition. The current study refutes previous evidence that PPI use is associated with a higher dementia risk, and it highlights that people with MCI or AD who require an acid suppressant may be more vulnerable to cognitive harms related to H2RA exposure than to exposure to a PPI.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ORCID

Walter Swardfager https://orcid.org/0000-0002-0030-8908

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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