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Research Article

The Effect of Cumulative Anticholinergic Use on the Cognitive Function of Older Adults: Results from the Personality and Total Health (PATH) Through Life Study

Malinee Neelamegam, PhD,[1,2] Janice Zgibor, PhD,[1] Henian Chen, MD, PhD,[1] Kathleen O'rourke, PhD,[1] Chighaf Bakour, MD, PhD,[1] Lakshminarayan Rajaram, PhD,[1] and Kaarin J. Anstey, PhD,[3,4,5]

[1]College of Public Health, University of South Florida, Tampa. [2]Yale School of Public Health, Yale University, New Haven, Connecticut. [3]Centre for Research on Ageing, Health and Wellbeing, Australian National University, Canberra. [4]School of Psychology, University of New South Wales, Sydney, Australia. [5]Neuroscience Research Australia, Sydney, Australia.

*Address correspondence to: Malinee Neelamegam, PhD, Yale School of Public Health, Yale University, 60 College Street, P.O. Box 208034, New Haven, CT 06520. E-mail: malinee.neelamegam@yale.edu

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Abstract

Background: Multiple comorbidities are common in older adults, resulting in polypharmacy that often includes medications with anticholinergic properties. These medications have multiple side effects, which are more pronounced in the older population. This study examined the association between the use of anticholinergics and changes in the cognitive function of older adults.

Methods: The study population consisted of 2,222 individuals aged 65–69 years at baseline from the Personality and Total Health (PATH) Through Life Study in Australia. Medication data were obtained from the Pharmaceutical Benefits Scheme (PBS). Cognitive measures were obtained from neuropsychological battery assessment. Exposure to cumulative anticholinergic use was quantified to a total standardized daily dose (TSDD). The association between change in cognitive measures between baseline and 4-year follow-up, and cumulative use of anticholinergic was assessed through generalized linear models.

Results: During the study period, 18.6% (n = 413) of participants filled at least one prescription for anticholinergics. Compared to those not on anticholinergics, participants on anticholinergics were more likely to be woman (62.7% compared to 45.1%) and spent lesser time engaging in vigorous physical activity (0.4 h/week compared to 0.9 h/week). Cumulative use of anticholinergic resulting in a TSDD exceeding 1,095 was significantly associated with poorer performance in Trail Making Test Part B (Model 1: β = 5.77, Model 2: β = 5.33, Model 3: β = 8.32, p < .01), indicating impairment in processing speed.

Conclusions: In our study, except for speed of processing, other cognitive domains measured were not affected by cumulative anticholinergic use over a 4-year period.

Keywords: Cognition, Cognitive aging, Medication

Multiple comorbidities are common among older adults. Studies show that the prevalence of comorbidities increases with age (1,2). Almost 62% of adults aged 65 years and above report having several chronic conditions (3). These conditions are inevitably managed with pharmaceutical agents, resulting in 90% of older adults using at least one prescribed medication, many of which contain anticholinergic agents (4). A significant number of both institutionalized older adults (approximately 40%) and community-dwelling older adults (50%) is prescribed at least one medication with anticholinergic properties (5,6).

Medications with anticholinergic properties function by inhibiting the transmission of acetylcholine in the central nervous system through their antagonistic effects on muscarinic receptors (7). In older adults, the association between the use of anticholinergics and central nervous system adverse effects is particularly important. In this population, the benefits of using medications with

strong anticholinergic properties are outweighed by the risks associated with these medications (8). Medications with anticholinergic properties result in adverse effects ranging from peripheral side effects such as dry mouth to more serious central nervous system side effects such as hallucinations (9).

The effects of medications with anticholinergic properties can be particularly profound in older adults due to age-related physiological changes in these individuals. These changes include increased permeability of the blood–brain barrier, fewer cholinergic receptors in the brain, and suboptimal hepatic and renal function (10). While earlier studies implied that anticholinergic-induced adverse effects were largely reversible upon discontinuation, more recent studies challenge this, demonstrating that anticholinergics may cause pathophysiological changes resulting in cognitive impairment that is not as easily reversible as previously suggested (11,12). Anticholinergic drugs also increase the risk of falls among older adults, particularly those with cognitive impairment (13). Older adults using anticholinergics are reported to have a higher incidence of Alzheimer's disease (AD) and dementia (14,15).

This study examined the impact of cumulative use of medications with anticholinergic properties on multiple cognitive domains among individuals aged 60 years and above over a period of 4 years. We also examined if the presence of apolipoprotein E (APOE) epsilon 4 (ε4) genotype modifies these associations.

Method

Study Design

The Personality and Total Health (PATH) Through Life Study is an ongoing longitudinal cohort study that assesses the lifespan course of multiple diseases and well-being among community-dwelling Australian adults. To date, the PATH study has followed three cohorts of participants, starting at ages 20–24 years, 40–44 years, and 60–64 years for approximately 19 years. The study participants are from three narrow age cohorts with birth years of 1975–1979 (the 20+ cohort), 1956–1960 (the 40+ cohort), and 1937–1941 (the 60+ cohort), respectively. Participants of all three cohorts were randomly sampled from the electoral rolls of the Australian Capital Territory (ACT) and Queanbeyan, Australia.

Wave 1 of the PATH study began between the years 2000 and 2002, and the three cohorts were followed at 4-year intervals, starting with the youngest cohort, with each cohort being interviewed successively over a 1-year period. Participation rates for follow-up visits across the cohorts range from 89% to 93%. Three substudies derived from subsamples of the main PATH study were conducted. These studies were the magnetic resonance imaging study, the Health and Memory study, and the Cardiovascular study. The PATH study design and study population were described previously (16).

Study Population

The study population consists of participants in the 60+ cohort of the PATH Through Life study. Data of these participants, from the first follow-up wave (Wave 2, year 2005/2006, n = 2,222) to the second follow-up wave (Wave 3, year 2009/2010, n = 1,973), were used. Data from Wave 1 of the PATH study was excluded in this analysis, as medication data were not available for Wave 1 of the PATH study. The Australian National University Ethics Committee approved the PATH Through Life study. Study participants provided written informed consent to participate in this study and to allow their data to be linked to the Australian Government Pharmaceutical Benefits Scheme (PBS) data.

Exposure Measure

Data on prescription medication use of study participants were obtained from the PBS. The PBS is a list of medications that can be dispensed to patients at a subsidized rate from the government of Australia. This service is available to all Australian citizens, permanent residents, and individuals visiting Australia from countries that have a reciprocal healthcare agreement with Australia. Eligible patients pay a nominal co-payment for medications on the PBS list, with the remaining cost of the medications being paid by the Australian government. Detailed explanation on the PBS and its use in pharmaco-epidemiology research is explained elsewhere (17,18).

The use of medications with anticholinergic properties between Wave 2 and Wave 3 of the PATH study was determined for the exposure measure. Medications with anticholinergic properties were identified using the Anticholinergic Risk Scale (ARS) (19) and the Anticholinergic Drug Scale (ADS) (20). In the ARS, medications are classified as having limited or no anticholinergic potential (rated 0), moderate anticholinergic potential (rated 1), strong anticholinergic potential (rated 2), or very strong anticholinergic potential (rated 3). In the ADS, medications are classified as having potential anticholinergic potential (rated 1), moderate anticholinergic potential (rated 2), and marked anticholinergic potential (rated 3). For this study, medications rated 1 on the ADS and 0 on the ARS were excluded. Medications not on either of the scale but classified as highly anticholinergic in the American Geriatrics Society 2012 Beers Criteria for potentially inappropriate medication use in older adults were included. Using data linkage to the PBS database, prescriptions filled for the selected medications by study participants during the study period were identified.

The exposure measure for medications with anticholinergic properties was the cumulative total standardized daily dose (TSDD). To derive the TSSD, the total dose of medications with anticholinergic properties in each prescription was calculated by multiplying medication strength with the number of tablets. This value was then divided by the medication-specific recommended minimum effective daily dose per day to derive the standardized daily dose (SDD) (21). For each study participant, SDD for all medications taken between Wave 2 and Wave 3 of the PATH study was summed to derive the cumulative TSDD. Study participants were then classified into categories of cumulative TSDD based on clinical significance (22). The list of medications used by participants in this study is presented in Table 1.

Outcome Measures

The outcome of interest in this analysis was change in participants' cognitive function from Wave 2 to Wave 3 of the PATH study. Cognitive function was assessed using multiple neuropsychology tests targeting key cognitive domains. The Mini-Mental State Examination (MMSE) was used to assess global cognition (23). Short-term memory was assessed through Immediate Recall and Delayed Recall using the California Verbal Learning Test (24). The Wechsler Memory Scale-Digit Span Backward was used to assess working memory (25) and the Symbol-Digit Modalities Test (26) was used to assess information processing. Verbal ability was assessed with Spot-the-Word Task (27) while psychomotor speed and information processing was assessed with Simple Reaction Time and Choice Reaction Time (28). Trail Making Test, parts A and B was

Table 1. List of Medications with Anticholinergic Properties Used by Study Participants in the 60+ Cohort of the PATH Through Life Study Between Wave 2 and Wave 3 (Minimum Effective Dose)(21)

Antihistamines	Antiparkinson agents
• Cyproheptadine (4 mg)	• Benztropine (0.5 mg)
• Cetirizine (5 mg)	• Trihexyphenidyl (6 mg)
• Loratadine (10 mg)	• Amantadine (100 mg)
Antidepressants	• Levodopa (100 mg)
• Amitriptyline (10 mg)	• Carbidopa (25 mg)
• Clomipramine (25 mg)	• Pramipexole (0.125 mg)
• Doxepin (10 mg)	• Entacapone (200 mg)
• Imipramine (10 mg)	Antipsychotics
• Nortriptyline (10 mg)	• Chlorpromazine (10 mg)
• Paroxetine (10 mg)	• Olanzapine (2.5 mg)
• Mirtazepine (7.5mg)	• Quetiapine (50 mg)
Antivertigo/antiemetic	• Haloperidol (0.25 mg)
• Prochlorperazine (15 mg)	• Risperidone (0.25 mg)
• Promethazine (50 mg)	Bladder antimuscarinics
• Metoclopramide (10 mg)	• Oxybutynin
Antacids and antihistamines	°Patch (3.9 mg)
• Ranitidine (150 mg)	°Oral (5 mg)
Gastrointestinal antispasmodics	Skeletal muscle relaxants
• Propantheline (22.5 mg)	• Baclofen (5 mg)
• Loperamide (4 mg)	Anticonvulsant
	• Carbamazepine (400 mg)

used to assess processing speed (29), and executive function while Purdue Pegboard Test was used to assess psychomotor speed (30).

Covariates

Multiple covariates linked to anticholinergic activity and cognitive function were included in the analysis. These included demographic factors such as age, sex, and years of education. Several lifestyle-related covariates were also included. Self-reported smoking status (categorized as current smoker, past smoker, and never smoked), alcohol consumption (assessed as drinks per week), and physical activity (categorized as hours of mild, moderate, and vigorous activity) were also included. Covariates representing clinical risk factors were self-reported stroke, diabetes, and family history of dementia, as well as depression assessed with the Patient Health Questionnaire (PHQ-9) (31). Hypertension status (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensives) and body mass index (BMI) (computed as weight [kg]/height [m^2]) were also included. To assess effect modification, the APOE epsilon 4 (ε4) genotype was added as a covariate of interest in this analysis. Genotyping for APOE variants in the PATH study population has been described elsewhere (32).

Statistical Analysis

Data analysis was completed in SAS (v.9.4, SAS Institute Inc., Cary, North Carolina). Demographic and health-related characteristics for the PATH study population at Wave 2, based on their exposure to medications with anticholinergic properties, were examined with bivariate analysis using *t*-tests and Fisher's Exact Test. Generalized Linear Models (GLM) were used to assess the association between medications with anticholinergic properties and change in cognitive function, and the effect modification of these associations by APOE-ε4 alleles. Three statistical models were used to assess these associations. Model 1 is an unadjusted model, while Model 2 adjusted for age, sex, and years of education. Additional

Table 2. Baseline Characteristics of Study Participants According to Anticholinergic Use: PATH Through Life Study, Wave 2, 2005–2006

	Not Using Anticholinergics (*N* = 1,809)	Using Anticholinergics (*N* = 413)
Demographic factors		
Age (years), mean (std)	66.6 (1.5)	66.6 (1.5)
Gender, *n* (%)***		
Male	993 (54.9)	154 (37.3)
Female	816 (45.1)	259 (62.7)
Race, *n* (%)		
White	1,738 (96.1)	395 (95.9)
Asian	40 (2.2)	12 (2.9)
Other	30 (1.7)	5 (1.2)
Education (years), mean (std)***	14.0 (2.7)	13.4 (2.6)
Marital status, *n* (%)		
Married	1,346 (74.4)	296 (71.7)
Unmarried living with a partner	67 (3.7)	9 (2.2)
Separated	30 (1.7)	15 (3.6)
Divorced	175 (9.7)	45 (10.9)
Widowed	148 (8.2)	40 (9.7)
Never married	42 (2.3)	8 (1.9)
Employment status, *n* (%)***		
Employed full-time	184 (10.2)	13 (3.1)
Employed part-time, looking for full-time employment	2 (0.1)	0 (0)
Employed part-time	327 (18.1)	55 (13.3)
Unemployed, looking for work	3 (0.2)	0 (0)
Not in the labor force	1,292 (71.5)	345 (83.5)
Lifestyle factors		
Smoking status, *n* (%)		
Never smoked	972 (53.8)	204 (49.5)
Past smoker	662 (36.6)	167 (40.5)
Current smoker	174 (9.6)	41 (10.0)
Alcohol consumption (drinks per week), mean (std)**	7.1 (8.7)	5.7 (7.5)
Physical activity (h/wk), mean (std)	7.8 (8.6)	8.2 (10.5)
Mild activity	2.8 (4.5)	2.7 (4.5)
Moderate activity	0.9 (0.4)	0.4 (1.2)
Vigorous activity***		
History of stroke, *n* (%)***		
Yes	39 (2.2)	23 (5.7)
No	1,731 (97.8)	379 (94.3)
History of diabetes, *n* (%)**		
Yes	163 (9.4)	55 (13.6)
No	1,576 (90.6)	349 (86.4)
History of hypertension, *n* (%)		
Yes	606 (34.1)	128 (31.4)
No	1,173 (65.9)	280 (68.6)
BMI, mean (std)***	26.6 (4.6)	27.7 (5.7)
Depression, *n* (%)***		
No depression	1,628 (91.5)	337 (83.8)
Subsyndromal depression	71 (4.0)	37 (9.2)
Minor depression	51 (2.9)	16 (4.0)
Major depression	30 (1.7)	12 (3.0)
Family history of dementia, *n* (%)		
Yes	282 (21.5)	58 (19.6)
No	1,031 (78.5)	238 (80.4)
Apolipoprotein ε4 allele, *n* (%)		
ε4–/ε4–	1,231 (72.2)	301 (75.8)
ε4+/ε4–	445 (26.1)	86 (21.7)
ε4+/ε4+	28 (1.6)	10 (2.5)

*Significance at $p < .05$. **Significance at $p < .01$. ***Significance at $p < .001$.

Table 3. Association Between Use of Anticholinergic Medications (Categorized According to Clinical Significance) and Cognitive Function (Mean and *SD*)

	MMSE[†]	Imm. Recall[‡]	Del. Recall[§]	Digit Back[‖]	
No use					
Baseline	29.2 (1.3)	6.9 (2.2)	6.1 (2.4)	5.2 (2.2)	
Follow-up	29.0 (1.3)	6.6 (2.2)	5.8 (2.4)	5.0 (2.2)	
Change	−0.2 (0.02)***	−0.3 (0.03)***	−0.3 (0.04)***	−0.2 (0.03)***	
TSDD 1–90					
Baseline	29.3 (1.2)	7.3 (2.3)	6.4 (2.3)	4.9 (2.1)	
Follow-up	29.0 (1.4)	6.9 (2.4)	6.2 (2.4)	4.7 (2.2)	
Change	−0.3 (0.1)***	−0.4 (0.1)**	−0.2 (0.1)	−0.2 (0.1)*	
TSDD 91–365					
Baseline	28.9 (1.3)	6.7 (2.5)	5.5 (2.7)	4.8 (2.1)	
Follow-up	28.7 (1.8)	6.0 (2.1)	5.3 (2.3)	4.6 (2.1)	
Change	−0.2 (0.2)	−0.7 (0.3)	−0.2 (0.3)	−0.2 (0.2)	
TSDD 366–1,095					
Baseline	29.2 (0.9)	7.1 (2.1)	6.1 (2.1)	5.1 (2.4)	
Follow-up	29.2 (1.0)	6.3 (2.1)	5.6 (2.1)	4.7 (2.2)	
Change	0 (0.1)	−0.8 (0.2)***	−0.5 (0.2)	−0.4 (0.2)	
TSDD >1,095					
Baseline	29.0 (1.3)	6.5 (2.4)	5.8 (2.6)	4.6 (2.1)	
Follow-up	28.8 (1.5)	6.2 (2.4)	5.4 (2.4)	4.6 (2.1)	
Change	−0.2 (0.1)*	−0.3 (0.1)*	−0.4 (0.1)***	0 (0.1)	
	Spot[¶]	SDMT[#]	PPEG (DH)[††]	PPEG (NDH)[‡‡]	PPEG (BH)[§§]
No use					
Baseline	52.9 (5.4)	49.5 (9.4)	13.5 (2.1)	12.7 (2.0)	10.4 (1.8)
Follow-up	52.9 (5.3)	47.2 (9.7)	12.2 (2.1)	11.6 (2.0)	9.4 (1.9)
Change	0 (0.1)***	−2.3 (0.1)***	−1.3 (0.03)***	−1.1 (0.03)***	−1.0 (0.03)***
TSDD 1–90					
Baseline	52.0 (5.0)	49.5 (9.5)	13.5 (2.1)	12.6 (1.9)	10.4 (1.8)
Follow-up	51.8 (5.3)	47.6 (9.1)	12.2 (2.2)	11.5 (2.0)	9.3 (1.9)
Change	−0.2 (0.3)	−2.1 (0.5)***	−1.3 (0.1)***	−1.1 (0.1)***	−1.1 (0.1)***
TSDD 91–365					
Baseline	51.4 (5.4)	49.5 (9.4)	13.9 (1.9)	12.9 (1.9)	10.7 (1.9)
Follow-up	51.3 (5.5)	46.0 (9.8)	12.2 (2.0)	12.3 (1.5)	9.5 (1.7)
Change	−0.1 (0.6)	−3.5 (1.1)**	−1.7 (0.2)***	−0.6 (0.2)**	−1.2 (0.2)***
TSDD 366–1,095					
Baseline	53.0 (5.3)	49.7 (6.8)	13.7 (2.2)	12.7 (1.9)	10.4 (1.9)
Follow-up	52.7 (6.1)	48.2 (6.6)	12.5 (1.9)	11.6 (2.0)	9.2 (1.9)
Change	−0.3 (0.6)	−1.5 (0.7)*	−1.2 (0.2)***	−1.1 (0.2)***	−1.2 (0.2)***
TSDD >1,095					
Baseline	51.3 (5.8)	46.6 (9.8)	12.9 (2.3)	12.0 (2.1)	10.1 (2.0)
Follow-up	51.2 (5.9)	44.3 (10.1)	11.5 (2.4)	11.0 (2.3)	8.8 (2.1)
Change	−0.1 (0.4)	−2.3 (0.4)***	−1.4 (0.1)***	−1.0 (0.1)***	−1.3 (0.1)***
	SRT[‖‖]	CRT[¶¶]	Trail A[##]	Trail B[†††]	
No use					
Baseline	276.0 (72.1)	328.4 (51.6)	35.0 (12.5)	81.4 (33.7)	
Follow-up	283.7 (68.7)	345.5 (57.5)	37.5 (14.4)	88.4 (37.8)	
Change	7.7 (1.0)***	17.1 (0.8)***	2.5 (0.2)***	7.0 (0.5)***	
TSDD 1–90					
Baseline	290.0 (93.7)	338.6 (65.5)	34.5 (9.4)	78.9 (31.5)	
Follow-up	286.1 (61.2)	346.9 (49.6)	36.8 (10.6)	86.0 (31.3)	
Change	−3.9 (4.2)	8.3 (3.1)**	2.3 (0.5)***	7.1 (1.7)***	
TSDD 91–365					
Baseline	270.2 (56.7)	329.1 (45.8)	32.5 (8.9)	77.7 (24.5)	
Follow-up	282.5 (55.1)	345.6 (43.7)	34.9 (9.4)	92.2 (36.1)	
Change	12.3 (6.2)	16.5 (4.9)**	2.4 (1.0)*	14.5 (3.4)***	
TSDD 366–1,095					
Baseline	272.1 (48.9)	331.0 (45.9)	33.4 (8.3)	81.2 (42.3)	
Follow-up	282.2 (44.1)	340.9 (41.2)	38.2 (12.4)	86.9 (30.4)	
Change	10.1 (4.8)*	9.9 (4.5)*	4.8 (1.1)***	5.7 (3.8)	
TSDD >1,095					
Baseline	306.7 (109.6)	342.7 (65.3)	37.6 (14.8)	88.0 (36.0)	

Table 3. Continued

	MMSE†	Imm. Recall‡	Del. Recall§	Digit Back‖
Follow-up	311.5 (94.9)	363.8 (74.9)	40.1 (19.0)	100.8 (42.3)
Change	4.8 (4.6)	21.1 (3.1)***	2.5 (0.8)**	12.8 (1.8)***

Notes: Measures for Trail A, Trail B, SRT, and CRT represent response time. Thus, positive values for change indicate a cognitive decline. All other measures (MMSE, Immediate Recall, Delayed Recall, Digit Back, Spot, SDMT, and PPEG) represent the number of items completed correctly (negative values for change indicate cognitive decline).

†Mini-Mental State Examination. ‡Immediate Recall. §Delayed Recall. ‖Digit Span Backwards Test. ¶Spot-the-Word Test. #Symbol Digit Modalities Test. ††Purdue Pegboard Test (Dominant Hand). ‡‡Purdue Pegboard Test (Nondominant hand). §§Purdue Pegboard Test (Both hands). ‖‖Simple Reaction Time. ¶¶Choice Reaction Time. ##Trail Making Test Part A. †††Trail Making Test Part B.

*Significance at $p < .05$ **Indicates significance at $p < .01$ ***indicates significance at $p < .001$.

to demographic factors in Model 2, Model 3 adjusted for lifestyle factors (smoking, alcohol consumption, and physical activity), clinical factors (stroke, diabetes, depression, family history of dementia, and BMI), and APOE-ε4 alleles. To minimize Type 1 error due to multiple comparisons, statistical significance was maintained at .01.

Results

Table 2 describes the characteristics of this study population at baseline based on their exposure to medications with anticholinergic properties. Of the 2,222 individuals, 413 filled at least one prescription for medication with anticholinergic properties during the study period. Participants on anticholinergics were more likely to be female compared to those not on anticholinergics (62.7% compared to 45.1%). Individuals not on anticholinergics had a lower BMI (26.6 compared to 27.7) and spent more time doing vigorous physical activity (0.9 hours/week compared to 0.4 hours/week). The percentage of participants with a history of stroke (5.7% compared to 2.2%), diabetes (13.6% compared to 9.4%), and depression (16.2% compared to 8.5%) was higher in the group exposed to anticholinergics.

Table 3 presents the mean change in the cognitive tests scores from baseline to follow-up according to the different levels of exposure to anticholinergics. There was generally a decline in the cognitive function in the study population from baseline to follow-up. This decline was seen across the comparison groups.

Table 4 shows the results from the assessment of the association between the use of medications with anticholinergic properties and cognitive function using Generalized Linear Models. Compared to those not on medications with anticholinergic properties, those with a cumulative exposure to anticholinergics exceeding a TSDD of 1,095 had significantly poorer performance in the Trail Making Test Part B (executive function; Model 1: $\beta = 5.77$, Model 2: $\beta = 5.33$, Model 3: $\beta = 8.32$, $p < .01$). This association is seen in all three models and remained significant after adjusting for demographic, lifestyle, and clinical factors.

Table 5 presents the effect modification of the association between the use of medications with anticholinergic properties (ACH) and cognitive function by the presence of one APOE ε-4 allele (APOE ε-4 +/–) and presence of both alleles (APOE ε-4 +/+). The interaction term (APOE ε-4 +/–)*ACH was not significantly associated with changes in cognitive function. However, we found that the interaction term (APOE ε-4 +/+)*ACH was significantly associated with a decline in Trail Making Test Part B. Among individuals with a cumulative exposure to anticholinergics resulting in a TSDD between 366 and 1,095, compared to individuals without APOE ε-4 alleles, individuals with both alleles a had a greater decline in their Trail Making Test Part B performance ($\beta = 78.82$, $p < .01$).

Discussion

In our study, we examined if the cumulative use of medications with anticholinergic properties over a period of 4 years is associated with a decline in cognitive function in the 60+ cohort of the PATH Through Life study. While most cognitive domains remained unaffected, we observed the significant effects of medications with anticholinergic properties on the change in the processing speed of participants in our study population. We found that cumulative use of anticholinergics over a period of 4 years, exceeding a TSDD of 1,095 is significantly associated with a decline in Trail Making Test Part B scores. This indicates that exposure to anticholinergics at this level impairs executive function and speed of processing in older adults. This association remained significant even after adjusting for multiple covariates. We also found that among those with a high level of exposure to anticholinergics, individuals who had two apolipoprotein E ε-4 alleles had a greater decline in their Trail Making Test Part B scores compared to those without the alleles. This finding is consistent with previous studies that found anticholinergics to affect executive function in both older adults (33) as well as among middle-aged adults (34). A recent study assessing the participants of the Longitudinal Aging Study Amsterdam (LASA) found that among older adults, higher levels of long-term cumulative exposure to anticholinergics was associated with impaired cognition (35).

In the United States, 6.8 million ambulatory care visits due to dementia are made annually, of which 43% of the patients are actively on at least one medication with anticholinergic properties (36). This is alarming as multiple studies show that medications with anticholinergic properties play a role in adversely affecting cognitive function in the older adults. This association exists in both community-dwelling older adults as well as those in residential care (37–39). Past studies demonstrate that anticholinergic use increases the risk of dementia (15). Among older adults, serum anticholinergic levels were associates with lower simple response times (40). In a study investigating the effect of anticholinergic use in an older population in France, the risk of dementia and AD was elevated among those with a history of chronic use of these medications (14). Chronic use of anticholinergics are also linked to AD pathology (41), accelerated decline in cognitive function (42), and greater dementia severity (43). In AD patients, the cholinergic system is particularly affected by the disease. Autopsy brain investigations of individuals with AD show compromised Acetylcholine receptor binding activity and reduced Acetylcholine (44,45). AD patients also have fewer cholinergic cells in their forebrain, pointing to the cholinergic loss in the disease (46).

Our study has several strengths. The PATH Through Life study provided a large community-dwelling older adult population for us

Table 4. Association Between Use of Anticholinergic Medications (Categorized According to Clinical Significance) and Cognitive Function (β Weights and *SE*)

	MMSE[†]	Immediate Recall	Delayed Recall	Digit Back[‡]	
TSDD 1–90					
Model 1	−0.13 (0.11)	−0.01 (0.18)	0.03 (0.18)	−0.10 (0.16)	
Model 2	−0.15 (0.11)	−0.04 (0.18)	0.01 (0.18)	−0.09 (0.16)	
Model 3	−0.18 (0.13)	−0.03 (0.21)	−0.01 (0.21)	−0.05 (0.18)	
TSDD 91–365					
Model 1	−0.03 (0.23)	−0.33 (0.37)	0.11 (0.38)	−0.05 (0.33)	
Model 2	−0.02 (0.23)	−0.32 (0.37)	0.12 (0.38)	−0.04 (0.33)	
Model 3	−0.06 (0.26)	−0.30 (0.44)	0.16 (0.45)	0.17 (0.42)	
TSDD 366–1,095					
Model 1	0.11 (0.23)	−0.42 (0.38)	−0.16 (0.37)	−0.26 (0.31)	
Model 2	0.09 (0.23)	−0.45 (0.38)	−0.17 (0.38)	−0.25 (0.31)	
Model 3	−0.23 (0.29)	−0.25 (0.49)	0.50 (0.48)	−0.18 (0.41)	
TSDD >1,095					
Model 1	0.03 (0.10)	0.04 (0.16)	−0.18 (0.16)	0.19 (0.14)	
Model 2	0.03 (0.10)	0.02 (0.16)	−0.20 (0.16)	0.20 (0.14)	
Model 3	−0.04 (0.11)	−0.10 (0.18)	−0.20 (0.18)	0.28 (0.18)	
	Spot[§]	SDMT[‖]	PPEG (DH)[¶]	PPEG (NDH)[#]	PPEG (BH)[††]
TSDD 1–90					
Model 1	−0.22 (0.22)	0.44 (0.53)	0.01 (0.18)	0.03 (0.18)	−0.12 (0.16)
Model 2	−0.23 (0.22)	0.30 (0.53)	0.02 (0.19)	−0.02 (0.18)	−0.08 (0.16)
Model 3	−0.19 (0.25)	0.27 (0.60)	0.01 (0.21)	−0.03 (0.21)	−0.03 (0.18)
TSDD 91–365					
Model 1	−0.26 (0.53)	−1.11 (1.08)	−0.50 (0.37)	0.56 (0.37)	−0.27 (0.32)
Model 2	−0.27 (0.53)	−1.13 (1.08)	−0.50 (0.37)	0.56 (0.37)	−0.28 (0.32)
Model 3	−0.52 (0.63)	−0.52 (1.28)	−0.49 (0.44)	0.60 (0.44)	−0.09 (0.38)
TSDD 366–1,095					
Model 1	−0.43 (0.45)	0.87 (1.04)	0.05 (0.34)	0.05 (0.33)	−0.23 (0.31)
Model 2	−0.44 (0.45)	0.78 (1.04)	0.05 (0.34)	0.07 (0.33)	−0.20 (0.30)
Model 3	−0.27 (0.55)	0.01 (1.24)	0.14 (0.43)	0.09 (0.40)	−0.15 (0.38)
TSDD >1,095					
Model 1	−0.15 (0.21)	0.03 (0.46)	−0.10 (0.16)	0.17 (0.14)	−0.25 (0.14)
Model 2	−0.15 (0.12)	−0.07 (0.47)	−0.10 (0.16)	0.16 (0.15)	−0.22 (0.14)
Model 3	−0.37 (0.25)	−0.35 (0.56)	−0.07 (0.19)	0.06 (0.17)	−0.31 (0.16)
	SRT[‡‡]	CRT[§§]	Trail A[‖‖]	Trail B[¶¶]	
TSDD 1–90					
Model 1	−11.53 (6.23)	−8.81 (4.03)*	−0.15 (1.13)	0.12 (2.66)	
Model 2	−11.34 (6.23)	−8.73 (4.05)*	0.24 (1.14)	−0.35 (2.69)	
Model 3	−7.67 (7.28)	−7.87 (4.77)	0.47 (1.31)	−0.26 (2.88)	
TSDD 91–365					
Model 1	4.55 (13.32)	−0.65 (8.69)	−0.14 (2.42)	7.47 (5.10)	
Model 2	4.77 (13.35)	−0.81 (8.73)	−0.26 (2.41)	7.00 (5.09)	
Model 3	13.41 (15.17)	2.56 (10.59)	−1.29 (2.88)	6.35 (6.16)	
TSDD 366–1,095					
Model 1	2.43 (12.86)	−7.21 (8.67)	2.33 (2.31)	−1.27 (4.92)	
Model 2	2.32 (12.93)	−7.07 (8.74)	2.71 (2.32)	−1.27 (4.91)	
Model 3	5.76 (15.77)	−4.09 (10.01)	3.04 (2.72)	−8.62 (5.97)	
TSDD >1,095					
Model 1	−2.93 (5.40)	4.03 (3.60)	−0.03 (1.04)	5.77 (2.27)**	
Model 2	−2.64 (5.39)	4.10 (3.64)	0.21 (1.04)	5.33 (2.27)**	
Model 3	−5.72 (6.30)	2.14 (4.26)	1.14 (1.24)	8.32 (2.67)**	

Notes: Measures for Trail A, Trail B, SRT, and CRT represent response time. Thus, positive values for change indicate a cognitive decline. All other measures (MMSE, Immediate Recall, Delayed Recall, Digit Back, Spot, SDMT, and PPEG) represent the number of items completed correctly (negative values for change indicate cognitive decline). Model 1 = unadjusted model. Model 2 = adjusted for age, sex, and education. Model 3 = Model 2 + smoking, alcohol consumption, physical activity, stroke, diabetes, hypertension, BMI, depression, and family history of dementia.

[†]Mini-Mental State Examination. [‡]Digit Span Backwards Test. [§]Spot-the-Word Test. [‖]Symbol Digit Modalities Test. [¶]Purdue Pegboard Test (Dominant Hand). [#]Purdue Pegboard Test (Nondominant hand). [††]Purdue Pegboard Test (Both hands). [‡‡]Simple Reaction Time. [§§]Choice Reaction Time. [‖‖]Trail Making Test Part A. [¶¶]Trail Making Test Part B.

*Significance at $p < .05$. **Significance at $p < .01$. ***Significance at $p < .001$.

Table 5. Effect Modification of the Association Between Use of Anticholinergic Medications (Categorized According to Clinical Significance) and Cognitive Function (β weights and *SE*) by Apolipoprotein (APOE) ε4 Allele

	MMSE[†]	Immediate Recall	Delayed Recall	Digit Back[‡]	
TSDD 1–90					
+/–	0.14 (0.31)	–0.12 (0.50)	–0.03 (0.51)	–0.03 (0.41)	
+/+	–0.44 (0.77)	–1.74 (1.30)	–1.22 (1.30)	–0.89 (1.11)	
TSDD 91–365					
+/–	0.11 (0.56)	–0.01 (0.85)	0.14 (0.85)	–0.49 (0.89)	
+/+	–0.45 (1.28)	–1.19 (2.14)	–2.54 (2.16)	–2.42 (1.88)	
TSDD 366–1,095					
+/–	0.87 (0.49)	–0.22 (0.82)	–1.49 (0.82)	–0.20 (0.81)	
+/+	1.64 (0.95)	–2.19 (1.60)	–3.76 (1.60)*	–0.79 (1.38)	
TSDD >1,095					
+/–	0.22 (0.25)	0.30 (0.37)	–0.10 (0.36)	–0.25 (0.36)	
+/+	0.92 (0.69)	0.47 (1.12)	0.29 (1.14)	0.27 (1.01)	
	Spot[§]	SDMT[‖]	PPEG (DH)[¶]	PPEG (NDH)[#]	PPEG (BH)[††]
TSDD 1–90					
+/–	–0.35 (0.57)	0.35 (1.35)	0.19 (0.54)	–0.07 (0.47)	–0.32 (0.42)
+/+	0.48 (1.51)	1.04 (3.70)	–1.56 (1.24)	–0.10 (1.89)	–0.19 (1.01)
TSDD 91–365					
+/–	0.43 (1.11)	–1.55 (2.74)	0.08 (0.81)	–0.36 (0.80)	–0.87 (0.72)
+/+	6.07 (2.53)*	3.94 (6.14)	0.72 (2.05)	–0.92 (1.95)	0.79 (1.71)
TSDD 366–1,095					
+/–	–0.13 (0.96)	1.14 (2.27)	–0.34 (0.86)	0.10 (0.74)	–0.10 (0.66)
+/+	0.24 (1.86)	4.75 (4.48)	0.64 (1.51)	–0.60 (1.43)	–0.003 (1.26)
TSDD >1,095					
+/–	0.83 (0.50)	1.87 (1.09)	0.08 (0.35)	0.18 (0.33)	0.21 (0.31)
+/+	0.99 (1.32)	–0.54 (3.21)	–1.63 (1.10)	0.09 (1.04)	0.71 (0.89)
	SRT[‡‡]	CRT[§§]	Trail A[‖‖]	Trail B[¶¶]	
TSDD 1–90					
+/–	–20.61 (18.09)	–9.23 (13.09)	–1.99 (3.24)	0.50 (6.46)	
+/+	–45.76 (43.55)	–4.74 (28.35)	–7.99 (7.95)	–6.01 (17.69)	
TSDD 91–365					
+/–	–25.71 (30.10)	–19.08 (21.84)	2.59 (5.35)	–4.48 (13.04)	
+/+	–101.84 (73.36)	–36.11 (47.42)	–5.72 (13.34)	33.96 (29.28)	
TSDD 366–1,095					
+/–	–21.33 (28.26)	–17.97 (19.48)	–1.89 (4.89)	12.13 (10.83)	
+/+	25.43 (54.00)	31.56 (34.90)	9.24 (9.83)	78.82 (21.30)**	
TSDD >1,095					
+/–	5.64 (12.49)	3.32 (8.81)	–3.38 (2.29)	–8.03 (5.11)	
+/+	13.91 (38.03)	11.56 (24.49)	–12.03 (6.99)	–30.56 (15.77)	

Notes: Measures for Trail A, Trail B, SRT, and CRT represent response time. Thus, positive values for change indicate a cognitive decline. All other measures (MMSE, Immediate Recall, Delayed Recall, Digit Back, Spot, SDMT, and PPEG) represent the number of items completed correctly (negative values for change indicate cognitive decline). +/– = presence of one APOE-ε4 allele. +/+ = presence of two APOE-ε4 alleles.

[†]Mini-Mental State Examination. [‡]Digit Span Backwards Test. [§]Spot-the-Word Test. [‖]Symbol Digit Modalities Test. [¶]Purdue Pegboard Test (Dominant Hand). [#]Purdue Pegboard Test (Nondominant hand). [††]Purdue Pegboard Test (Both hands). [‡‡]Simple Reaction Time. [§§]Choice Reaction Time. [‖‖]Trail Making Test Part A. [¶¶]Trail Making Test Part B.

*Significance at $p < .05$. **Significance at $p < .01$. ***Significance at $p < .001$.

to study. This allowed us to investigate the impact of these medications on older adults without severe comorbidities, which would have been strong confounders in the analysis. The PATH Through Life study measures cognitive function through a neuropsychology battery assessment approach, allowing us the opportunity to study changes in multiple cognitive domains over time. The PATH Through Life study also collects data on multiple factors, giving us the opportunity to adjust for important covariates in our analysis. One such important variable was the APOE epsilon 4 (ε4) genotype. We were able to assess whether APOE ε-4 alleles modified the association between the use of anticholinergics and cognitive function. By obtaining medication information from a database such as the PBS, we were able to objectively quantify anticholinergic exposure according to reliable standards of exposure measures, eliminating recall bias that may have happened if we had to use self-reported medication use (47).

There are some limitations to this study. The accuracy of anticholinergic burden measured in this study is limited by the use of a medication dispensing database for exposure measurement. The PBS database captures information on medications that are prescribed and filled. It does not provide information on medication consumption and adherence. Furthermore, it does not capture information on medications purchased over the counter, many of which can have anticholinergic properties (48). We took a conservative approach in determining exposure to medications with anticholinergic properties. Individuals with no prescription information during the exposure window were classified as not exposed to anticholinergics. These limitations may have resulted in underrepresented

exposed individuals in this study and resulted in underestimation of the measure of effect. The time period between the baseline and a follow-up visit is short, particularly given that cognitive impairment is often insidious in nature with onset occurring much earlier before symptoms are apparent. Therefore, the exact point of onset of the disease and accurate predisease exposure is challenging to determine. As such, there is a possibility of reverse causality in this study. Many co-existing conditions requiring medications with anticholinergic properties may also be associated with an increased risk of cognitive impairment. In our study, we were only able to adjust for a limited number of self-reported medical conditions and may not have addressed all concerns on indication bias.

This study provides key findings to support the need for further research. Studies with a longer follow-up period will allow us to see the impact of a longer cumulative dose of these medications on cognitive function. Neuroimaging studies with a longer follow-up period will also allow us to detect changes in structural changes in the brain due to anticholinergic exposure. Future analysis should focus on the effect of the different classes of anticholinergics to investigate if the cumulative use of anticholinergics from different medication classes produces significantly different effects on the cognitive and volumetric outcomes we have examined in our study. Due to the importance of the frontal lobe in the cholinergic system, it would be informative to study changes in the frontal lobe of the brain when investigating the effects of cumulative anticholinergic.

As potential inappropriate use of anticholinergics is a modifiable risk factor for cognitive impairment and other adverse effects in older adults, steps to prevent misuse can greatly reduce the related negative outcomes. As exposure to medications with anticholinergic properties is not limited to prescription medications, prescribing guidelines alone will not sufficiently reduce the use of these medications among older adults. Health promotion activities to support healthy aging must include steps to educate and create awareness among older adults on the effects of their medications. Health education improves health behavior and empowers older adults to practice good self-management of their conditions (49). Increasing awareness among older adults and their caregivers about the potential adverse effects of their medications will empower them to advocate for their care, engage actively in shared decision making regarding the management of their conditions, and potentially reduce the use of these medications, especially for conditions where alternative therapies and treatment modalities are available.

Conclusion

This study showed that while most cognitive domains remained unaffected, high cumulative exposure to medications with anticholinergic properties had a significant negative effect on executive function and processing speed in older adults. Although multiple guidelines have cautioned the use of medications with anticholinergic properties in older adults, their use in this population is unavoidable due to the multiple comorbidities, that are managed with these medications. However, prescribers should be aware of the adverse effects of these medications and seek alternative treatment options when available. In the event the use of medications with anticholinergic properties is mandatory in older adults, prescribers must strive to treat older patients with the lowest effective dose of these medications. As multiple over the counter medications have anticholinergic properties, it is vital to create awareness among older adults about the potential modifiable risks of these medications. Future studies on the impact of the different classes of medications with anticholinergic properties in older adults will aid in the understanding of the mechanisms of these medications on cognition and structural changes in the brain in this vulnerable population.

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Author Contributions

M. Neelamegam planned the study, conducted the data analysis, and wrote the article. K.J. Anstey planned the study, particularly for the methodology of cognitive assessment, and contributed to revising the article. J. Zgibor contributed to revising the article and helped plan the methodology for exposure measurement. H. Chen, L. Rajaram, K. O'rourke, and C. Bakour provided guidance for statistical analysis and contributed to revising the article.

Conflict of Interest

None reported.

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