



Association between anticholinergic burden and cognitive impairment in community-dwelling older adults

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Background

As individuals aging, acetylcholine production significantly declines, leading to increased receptor sensitivity, cholinergic neuron damage, and slower drug metabolism. These changes make older adults more vulnerable to the anticholinergic drugs. Between 30% and 50% of medications for older adults possess anticholinergic effects, raising risks for dementia, falls, and mortality. This longitudinal study explores the association between anticholinergic burden and cognitive impairment, aiming to facilitate earlier dementia detection and optimize pharmacological management for older adults.

Methods

As part of the Taiwan Initiative for Geriatric Epidemiological Research (TIGER), this prospective cohort study enrolled non-demented community-dwelling adults between 2011 and 2013, with follow-up extending to 2022.

- **Inclusion criteria**
 - Older adults aged ≥ 65 years
- **Exclusion criteria**
 - Medication for dementia
 - Suspected dementia (The Taiwanese version of Montreal Cognitive Assessment [MoCA-T] score ≤ 21)
 - Brain tumor
 - Stroke
 - Traumatic brain injury or loss consciousness ≥ 30mins
- **Exposure**
 - Using the Anticholinergic Cognitive Burden (ACB) scale to score each drug and then totaled these values to represent the overall anticholinergic burden
- **Outcome measures**
 - Global cognition (MoCA-T score)
 - Domain-specific cognitive functions (memory, attention, executive function, and verbal fluency)

Generalized Linear Mixed Models (GLMMs) were used to evaluate the longitudinal association between medication burden and global or domain-specific cognitive decline.

Results

Table 1. Baseline characteristics of study participants (2011-2013)

	Overall (n = 536)	No drugs (n = 143)	No anticholinergic burden (n = 281)	Anticholinergic burden (n = 112)	p -value
Mean (SD)					
Age (years)	72.68 (5.35)	70.78 (4.69)	73.20 (5.49)	73.79 (5.24)	<0.001
BMI (kg/m ²)	23.90 (2.96)	23.51 (2.83)	23.89 (2.93)	24.44 (3.13)	0.047
Education (years)	13.64 (3.74)	13.81 (3.60)	13.79 (3.70)	13.02 (3.99)	0.256
IL-6 (pg/mL)	2.54 (2.37)	2.47 (2.44)	2.47 (2.30)	2.78 (2.44)	0.416
Homocysteine (μmol/L)	11.04 (3.48)	10.47 (2.74)	11.05 (3.58)	11.76 (3.94)	0.013
Total ACB score	0.34 (0.90)	0 (0)	1.63 (1.33)		<0.001
Total number of drugs	2.65 (2.61)	0 (0)	2.94 (1.85)	5.29 (2.80)	<0.001
N (%)					
Female	287 (53.54)	87 (60.84)	147 (52.31)	53 (47.32)	0.083
APOE ε4 carrier	84 (15.76)	28 (19.58)	41 (14.75)	15 (13.39)	0.323
Cigarette smoking	87 (16.23)	19 (13.29)	43 (15.30)	25 (22.32)	0.126
Alcohol drinking	108 (20.15)	20 (13.99)	56 (19.93)	32 (28.57)	0.016
Annual household income					0.498
< 9.3K USD	88 (17.46)	22 (16.18)	44 (16.54)	22 (21.57)	
9.3-24.8K USD	130 (25.79)	35 (25.74)	67 (25.19)	28 (27.45)	
24.8K-31K USD	73 (14.48)	16 (11.76)	39 (14.66)	18 (17.65)	
> 31K USD	213 (42.26)	63 (46.32)	116 (43.61)	34 (33.33)	
Comorbidities					
Hypertension	266 (49.63)	24 (16.78)	161 (57.30)	81 (72.32)	<0.001
Hypercholesterolemia	227 (42.43)	48 (33.57)	126 (45.00)	53 (47.32)	0.040
Diabetes	81 (15.14)	11 (7.69)	46 (16.43)	24 (21.43)	0.007
Heart disease	143 (26.68)	20 (13.99)	73 (25.98)	50 (44.64)	<0.001
Chronic respiratory disease	53 (9.89)	11 (7.69)	25 (8.90)	17 (15.18)	0.100
Chronic arthritis	165 (30.84)	48 (33.57)	87 (30.96)	30 (27.03)	0.533
Osteoporosis	163 (33.82)	47 (35.34)	82 (32.67)	34 (34.69)	0.853
Parkinson disease	5 (0.93)	1 (0.70)	1 (0.36)	3 (2.68)	0.092
Depressive symptoms	43 (8.02)	6 (4.20)	15 (5.34)	22 (19.64)	<0.001

Abbreviation: ACB, Anticholinergic Cognitive Burden; BMI, body mass index; APOE, apolipoprotein E; IL, interleukin-6; USD, United States dollar; SD, standard deviation

Table 2. Association between anticholinergic burden and cognitive impairment over time (2011-2022)

Variables	Global cognition (MoCA-T score)	Memory			
		Immediate theme recall	Immediate free recall	Delayed theme recall	Delayed free recall
Total ACB score	-0.176 (-0.419, 0.066)	-0.064 (-0.168, 0.040)	-0.105 (-0.210, -0.000)	-0.097 (-0.202, 0.007)	-0.129 (-0.239, -0.020)
Total ACB score * time	0.006 (-0.039, 0.050)	0.003 (-0.016, 0.022)	0.010 (-0.006, 0.025)	0.004 (-0.013, 0.022)	0.013 (-0.003, 0.030)

Variables	Executive function		Attention		Verbal fluency
	Trail making test A	Trail making test B	Digit span forward	Digit span backward	
Total ACB score	-0.060 (-0.154, 0.033)	0.012 (-0.089, 0.113)	-0.062 (-0.159, 0.036)	-0.017 (-0.114, 0.079)	-0.069 (-0.169, 0.031)
Total ACB score * time	0.001 (-0.011, 0.014)	0.002 (-0.011, 0.015)	-0.005 (-0.021, 0.011)	-0.020 (-0.035, -0.004)	0.001 (-0.012, 0.014)

Abbreviation: ACB, Anticholinergic Cognitive Burden; MoCA-T, The Taiwanese version of Montreal Cognitive Assessment

Generalized linear mixed models were used to estimate β for cognition adjusted for age, sex, education year, APOE ε4 status, depressive symptoms, follow-up time, practice effect, income, hypertension, diabetes, and biomarkers (interleukin-6, homocysteine).

Table 3. Association between anticholinergic burden and cognitive impairment over time stratified by sex

Cognition	Anticholinergic burden	Men	Women	<i>P</i> _{interaction}
β(95% CI)				
Immediate free recall	Total ACB score	-0.119 (-0.250, 0.012)	0.019 (-0.172, 0.210)	0.031
	Total ACB score * time	0.005 (-0.014, 0.024)	0.033 (0.001, 0.065)	
Delayed free recall	Total ACB score	-0.124 (-0.260, 0.013)	-0.066 (-0.269, 0.137)	0.016
	Total ACB score * time	0.006 (-0.013, 0.025)	0.046 (0.013, 0.080)	
Digit span backward	Total ACB score	-0.011 (-0.122, 0.099)	0.060 (-0.131, 0.251)	0.287
	Total ACB score * time	-0.022 (-0.040, -0.004)	-0.010 (-0.045, 0.024)	

Abbreviation: ACB, Anticholinergic Cognitive Burden

Generalized linear mixed models were used to estimate β for cognition adjusted for age, sex, education year, APOE ε4 status, depressive symptoms, follow-up time, practice effect, income, hypertension, diabetes, and biomarkers (interleukin-6, homocysteine).

Table 4. Association between anticholinergic burden and cognitive impairment over time stratified by age

Cognition	Anticholinergic burden	Age < 75	Age ≥ 75	P _{interaction}
		β (95% CI)		
Immediate free recall	Total ACB score	-0.084 (-0.203, 0.035)	-0.077 (-0.267, 0.113)	0.146
	Total ACB score * time	-0.009 (-0.033, 0.016)	0.016 (-0.012, 0.045)	
Delayed free recall	Total ACB score	-0.090 (-0.210, 0.030)	-0.133 (-0.332, 0.067)	0.039
	Total ACB score * time	-0.016 (-0.040, 0.009)	0.026 (-0.004, 0.055)	
Digit span backward	Total ACB score	-0.006 (-0.127, 0.115)	-0.014 (-0.182, 0.154)	0.892
	Total ACB score * time	-0.023 (-0.050, 0.003)	-0.022 (-0.048, 0.004)	

Abbreviation: ACB, Anticholinergic Cognitive Burden

Generalized linear mixed models were used to estimate β for cognition adjusted for age, sex, education year, APOE ε4 status, depressive symptoms, follow-up time, practice effect, income, hypertension, diabetes, and biomarkers (interleukin-6, homocysteine).

Table 5. Association between anticholinergic burden and cognitive impairment over time stratified by education year

Cognition	Anticholinergic burden	Education year < 12	Education year ≥ 12	<i>P</i> _{interaction}
β(95% CI)				
Immediate free recall	Total ACB score	0.134 (-0.265, 0.532)	-0.131 (-0.242, -0.020)	0.021
	Total ACB score * time	0.056 (-0.004, 0.116)	0.006 (-0.010, 0.023)	
Delayed free recall	Total ACB score	0.133 (-0.276, 0.543)	-0.158 (-0.274, -0.041)	0.012
	Total ACB score * time	0.064 (0.008, 0.120)	0.010 (-0.007, 0.027)	
Digit span backward	Total ACB score	0.212 (-0.147, 0.570)	-0.044 (-0.146, 0.059)	0.345
	Total ACB score * time	-0.008 (-0.063, 0.047)	-0.021 (-0.037, -0.004)	

Abbreviation: ACB, Anticholinergic Cognitive Burden

Generalized linear mixed models were used to estimate β for cognition adjusted for age, sex, education year, APOE ε4 status, depressive symptoms, follow-up time, practice effect, income, hypertension, diabetes, and biomarkers (interleukin-6, homocysteine).

Conclusion

Over an 8-year follow-up, baseline higher anticholinergic burden was associated with poor memory performance, with women exhibiting greater vulnerability to these effects. With advancing time, a one-unit increase in anticholinergic burden was associated with a decline in attention performance. Consequently, when prescribing anticholinergic medications to older adults, it is crucial to carefully weigh the benefits against potential cognitive risks and explore safer alternatives whenever possible.

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