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Research Article

Anticholinergic Drug Induced Cognitive and Physical Impairment: Results from the InCHIANTI Study

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Abstract

Background: The aims of this study were to evaluate the relationship between anticholinergic drug burden (ACB) cognitive impairment, physical frailty, and cognitive frailty, and to determine if ACB is predictive of these phenotypes when modeled with biological and genomic biomarkers.
Methods: In a retrospective cohort study, a total of 1,453 adults aged 20–102 years were used to examine ACB as a predictor for cognitive impairment, physical frailty, and cognitive frailty. Anticholinergic burden is examined as a predictor for all phenotypes in a cross-sectional analysis using logistic, ordinal regression models, and Extreme Gradient Boosting for population predictive modeling.
Results: A significant association was found between ACB and cognitive decline ($p = .02$), frailty ($p < .001$), and cognitive frailty ($p < .001$). The odds of cognitive impairment increased by 1.21 (95% confidence interval [CI] = 1.06–1.37, $p < .001$), odds of being frail increased by 1.33 (95% CI = 1.18–1.50, $p < .001$), and odds of having cognitive frailty increased by 1.36 (95% CI = 1.21–1.54, $p < .001$). Population modeling results indicated ACB score as one of the stronger predictors for cognitive impairment, physical frailty, and cognitive frailty with area under the curves ranging from 0.81 to 0.88.
Conclusions: Anticholinergic medications are a potentially modifiable risk factor for the prevention of cognitive and physical decline. Identification of reversible causes for cognitive and physical impairment is critical for the aging population. These findings encourage new research that may lead to effective interventions for deprescribing programs for the prevention of cognitive and physical decline in older adults.

Keywords: Cognition, Frailty, Medication

Older adults are especially susceptible to polypharmacy and medication adverse risks due to declines in physiological reserve, reduced liver and kidney function required to metabolize medications, and increased central nervous system sensitivity to medications (1). A decline in physiologic reserve coupled with the use of anticholinergic medicines increases the risk for impaired functional and cognitive performance (2–4). Despite increasing evidence of adverse outcomes, the prescribing of medications with high anticholinergic burden (ACB) to community-dwelling older adults has increased with reports of 20%–50% taking medications with anticholinergic activity (5–7). Medications with anticholinergic properties commonly used to treat multiple chronic diseases have been associated with cognitive and physical impairment in older adults (8–10).

Anticholinergic medications block the neurotransmitter acetylcholine in the central and peripheral nervous system, selectively blocking acetylcholine from binding to the muscarinic receptors in the brain (6,11). Additionally, there is growing evidence that anticholinergics affect older adults in greater proportion due to the ability of these medications to permeate the blood–brain barrier (9). Anticholinergic burden is considered to be the cumulative effect on an individual taking one or more medications with anticholinergic activity confounded by age-related pharmacokinetic and pharmacodynamic changes (1,4,6). Higher anticholinergic burden can occur with specific medications known to have high anticholinergic activity or with an accumulation of medications with low, medium, and high anticholinergic burden (12,13). An increase in circulating anticholinergic activity causes inhibition of acetylcholine transmission to the central nervous system suggesting a cholinergic deficit that is hypothesized to be involved in causing impaired cognitive and motor function (14). Systematic reviews on current anticholinergic burden scales have all shown an association between higher anticholinergic burden and adverse outcomes; cohort studies have mainly focused on cognitive outcomes (4,12). Currently, there are seven expert-based anticholinergic rating scales for which studies have used scales with different models of incident cognitive decline (3,15). When compared, four measures of anticholinergic burden with variations in defining drug exposure were associated with memory decline over a 1-year period: Drug Burden Index (DBI-Ach) (16), Anticholinergic Cognitive Burden scoring scale (ACB-scale) (17), Anticholinergic Drug Scale (ADS) (18), and Anticholinergic Risk Scale (ARS) (15,19). Less understood is the effect anticholinergic drug burden has on physical frailty and individuals who present with both cognitive impairment and physical frailty (4).

Although there is evidence to support the relationship between physical function and higher anticholinergic burden, the methods for measuring physical functioning have focused on activities of daily living (ADLs) and instrumental activities of daily living (IADLs) without controlling for confounding health factors contributing to the outcome (4,12). Changes in ADLs and IDLs can be affected by multiple psychosocial and physiological factors that are not a direct measure of disease. A recent study found a significant association of anticholinergic burden with gait and impaired balance measured by the timed-up and go (TUG), functional reach (FR), and grip strength (GS) assessments (20). Frailty as defined by the Cardiovascular Heart Study (CHS) is a disease process and a non-normal process of aging (21). The CHS frailty phenotype includes decline in lean body mass, strength, endurance, balance, walking performance, and low activity (21). Additionally, there is growing evidence for a shared relationship between cognitive impairment and physical frailty (22–24). The International Consensus Group organized by the International Academy on Nutrition and Aging (I.A.N.A) and the International Association of Gerontology and Geriatrics (I.A.G.G) which convened in 2013 to identify related domains of physical frailty and cognition, termed this relationship as "cognitive frailty" (23). However, further research is needed to understand the shared mechanisms behind the dynamic association of these two constructs. Studies thus far have primarily used the Mini-Mental State Examination (MMSE) to measure cognitive impairment which as a composite test does not capture distinct areas of cognitive function such as processing speed, attention, psychomotor speed, abstraction, flexibility, ability to execute and modify a plan of action (25).

The goal of this study was to use logistic and ordinal regression models to determine the relationship between anticholinergic burden and three phenotypes: cognitive impairment defined by the MMSE and Trail Making Tests (TMT), part A and B, physical frailty, and individuals with cognitive frailty as defined by the International Consensus Group (I.A.A.A. /I.A.G.G.) (23). Additionally, we included anticholinergic burden in a population-based predictive model to determine if anticholinergic burden is predictive when modeled with additional measures of disease such as protein and genomic biomarkers for frailty and cognitive impairment thereby evaluating ACB with confounding disease processes (26).

Methods

Participants

The subjects in the present study were participants in *Invecchiare in Chianti* (Aging in Chianti, "InCHIANTI Study"). InCHIANTI is a prospective population-based study of 1,453 adults aged 20–102 years randomly selected from two towns in Tuscany, Italy using a multistage stratified sampling at baseline from 1998 to 2000 (27). All aspects of the InCHIANTI research were approved by the ethics committees at the institutions responsible for data collection, and this secondary study was approved by the ethics committee at *Centre de recherché Clinique du CHUS*. During the initial InCHIANTI baseline 90-minute interview, information was collected on demographic and clinical characteristics for the three phenotypes and baseline medications taken regularly in the prior 15 days to determine anticholinergic drug burden. The name of the drug, preparation, and dosage were collected from medication boxes or bottles including over the counter vitamins, food supplements, sleeping pills, or laxatives. Initial medication information was converted from the brand name to the active ingredient.

Anticholinergic Drug Burden Assessment

The ACB scoring scale was developed to evaluate the effect of ACB medications on cognitive function (3,13). The anticholinergic properties of each medication were quantified using the ACB scale based on each drug's serum anticholinergic activity (28). To determine ACB scores, each participant's medications were assigned points (0, 1, 2, 3) according to the published 2012 update and summed for a total anticholinergic burden score. Higher scores indicate higher anticholinergic properties. An example of medications with ACB scores include: Amitriptyline = 3, Amantadine = 2, and Atenolol = 1. The ACB scale has identified medications with anticholinergic properties that have correlated with a 0.33-point decline in the MMSE score over 2 years (29).

Cognitive Assessment

The neuropsychological tests included the MMSE as a test of general cognition and Trail Making Test, part A and B (TMT). The TMT testing was included to further explore distinct areas of cognitive function. Attention and psychomotor speed was assessed using the TMT-A and executive function assessed using TMT-B; scoring is based on time in seconds to completion with a score range of 0 to 300 seconds (30,31). Normative data for time to complete the TMT tests in seconds is stratified by age and education (31). Additionally, the neuropsychological profile for individuals with cognitive frailty is considered to be different from those with frailty or cognitive impairment alone with recent findings of lower performance on TMT tests (32). The Center for Epidemiologic Studies Depression Scale (CES-D) self-report scale was used to measure depressive symptoms. The CES-D has been used extensively in epidemiologic studies for depression and physical function displaying similar reliability,

validity, and factor structure across a diverse demographic (33). Response ranges from 0 to 60, with cutoff points 16 or greater indicating depression (33).

Frailty Assessment

Frailty measures included the number of frailty symptoms as defined by the cardiovascular health study (CHS). The CHS phenotypic frailty criteria allows for a continuous scoring system versus a nominal system because it can capture the multidimensional nature of frailty (22). The components have concurrent and predictive validity with hazard ratios (HR) ranging from 1.82 to 4.46 ($p < .05$) for outcomes that include incident disease, hospitalization, falls, disability and mortality in community-dwelling older adults (21). InCHIANTI defined frailty using five criteria, exhaustion, slowness, low physical activity, weakness, and unintentional weight loss on all subjects ≥65 years. Detailed description of the data collection and frailty classifications have been previously published (27,34).

Phenotypic Classification

The MMSE score and the TMT part A and B were used to define two phenotypic classifications for cognitive impairment. Absence of cognitive impairment is defined as a score of 24–30 on the education adjusted MMSE (35–37). Frailty is characterized by individuals with one or more of the frailty criteria (21). The binomial model combines prefrail and frail (≥ 1 criterion). Cognitive frailty is defined as individuals with cognitive impairment and one or more of the frailty criteria (32).

- Robust no physical frailty and absence of cognitive impairment
- Robust no physical frailty with cognitive impairment (MMSE ≤ 23)
- Frail (≥ 1 criterion) and absence of cognitive impairment
- Frail (≥ 1 criterion) and cognitive impairment (MMSE ≤ 23)

Additional phenotypic classification included moderate or severe disease defined by the MMSE to characterize 24–30 as normal cognition, a score of 23–18 as moderate cognitive impairment (combined mild and moderate degree of impairment), and a score ≤ 17 as severe cognitive impairment (35,36).

- Robust no physical frailty and absence of cognitive impairment
- Robust no physical frailty with moderate cognitive impairment (MMSE = 18–23)
- Robust with no physical frailty with severe cognitive impairment (MMSE ≤ 17)
- Prefrail (1–2 criteria) and absence of cognitive impairment
- Frail (≥3 criteria) and absence of cognitive impairment
- Prefrail (1–2 criteria) and with moderate cognitive impairment (MMSE = 18–23)
- Frail (≥3 criteria) and with moderate cognitive impairment (MMSE = 18–23)
- Prefrail (1–2 criteria) and severe cognitive impairment (MMSE = ≤ 17)
- Frail (≥3 criteria) and severe cognitive impairment (MMSE ≤ 17)

Additional neuropsychological testing (TMT-A and B) was used for evaluating the effect of ACB on psychomotor speed, attention and executive functioning. These specific memory domains have been found to be uniquely effected in individuals presenting with cognitive frailty (32). TMT-A and B cut off scores for cognitive impairment are based on established cut off norms (31,38).

- Robust no physical frailty and absence of cognitive impairment
- Robust no physical frailty with cognitive impairment (both Trail A ≥ 78 and Trail B ≥ 106)
- Frail (≥1 criterion) and cognitive impairment (both Trail A ≥ 78 and Trail B ≥ 106)
- Frail (≥1 criterion) and cognitive impairment (both Trail A ≥ 78 and Trail B ≥ 106)

Numbers of participants were insufficient for statistical analysis to include cognitive impairment categorized into levels of prefrail and frail with moderate and severe phenotype with the TMT.

Statistical Analyses

In this cross-sectional study, we used logistic and ordinal regression to investigate the relationship between anticholinergic burden and all three outcomes. Covariates were selected to control for potential confounding effects. Demographic covariates included gender, age, and level of education. Disease processes considered as confounders included baseline diagnosis of dementia ($n = 82$), vascular dementia ($n = 41$), depression ($n = 412$), and Parkinson's disease ($n = 16$) and were included in the models as binary covariates. McFadden's pseudo-R^2 was used to determine model fit; R^2 values of 0.2 to 0.4 represent a good model fit (39).

Population Prediction Analysis

Anticholinergic burden was included in a population-based predictive model study to determine if anticholinergic burden is predictive of cognitive impairment, physical frailty, and individuals with both cognitive impairment and physical frailty. The population predictive model incorporates additional measures identified through a previously published systematic review of literature which identified shared biological protein and genomic biomarkers for cognitive impairment and frailty; thereby evaluating ACB with confounding disease processes (26,40). Predictive modeling via ensemble learning using *xgboost* allowed for better accuracy by building multiple models, each of which learns to improve upon the errors of a prior model producing a final model that reflects the complex interactions between biological processes (ie, protein and genetic biomarkers) on cognitive impairment and frailty. Parameters for the *xgboost* model included a stepsize eta of = "0.3", rounds = 5–200, max depth = "10", nthread = "12", objective = "binary:logistic", evaluation metric = "auc", gamma = default ="0" to control the number of trees and prevent overfitting (41). Bivariate analyses included nonparametric Kruskal–Wallis *t* tests to assess differences between groups; medians and maximum quantiles are reported for healthy controls and three phenotypes. Next, Bonferroni correction was conducted to adjust for multiple comparisons; adjusted *p*-values are reported. All statistical analyses were carried out using R V. 3.2.1. R packages included "*glm2*"-Fitting Generalized Linear Models, "*Ordinal*"-Regression Models for Ordinal Data, and "*xgboost*"-Extreme Gradient Boosting (41–43). Additional details on the population predictive model results and statistical methods beginning with model development in the InCHIANTI data set used to train and test classifiers, complete internal validation, calibration of the model, and reproducible R code are available at GitHub Laboratory of Neurogenetics National Institute of Aging NIH, Population Predictive Model InCHIANTI Study repository; https://github.com/neurogenetics/Population-Predictive-Model-InCHIANTI-Study (40).

Results

For the current study, a total of 2,883 baseline medications were used to analyze the anticholinergic burden effect on 1,155 individuals ≥65 years of age with cognitive impairment, physical frailty, and individuals presenting with cognitive frailty; Table 1 describes the characteristics of the participants by phenotype and the percent of individuals with a total daily ACB score, which ranged from 0 to 9. Distribution

of anticholinergic burden score by phenotype and differences between healthy control and phenotype are shown in Table 2. Tables displaying results for the top predictive features from the *xgboost* predictive modeling study are published on GitHub Population Predictive Model InCHIANTI Study repository; https://github.com/neurogenetics/Population-Predictive-Model-InCHIANTI-Study (40).

There was a significant association between anticholinergic burden and cognitive impairment ($p = .02$), frailty ($p < .001$), and individuals with cognitive frailty ($p < .001$) compared with healthy controls. Additionally, with odds of cognitive impairment increased by 1.21 (95% confidence interval [CI] = 1.06–1.37, $p < .001$), the odds of being frail increased by 1.33 (95% CI = 1.18–1.50, $p < .001$), and odds of having cognitive frailty increased by 1.36 (95% CI = 1.21–1.54, $p < .001$) compared to healthy controls. McFadden pseudo-R^2 indicated a good fit for all models: cognitive impairment (0.46), frailty (0.30), and cognitive frailty (0.37). Logistic and ordinal regression results are presented in Tables 3 and 4.

Similarly, there was a significant association found between ACB score and cognitive impairment when measured with the TMT-A and TMT-B without adjusting for covariates. When including the covariates age, gender, and baseline dementia individually in the models with only ACB score for TMT-B or age and gender for TMT-A, ACB was no longer significant. Additionally, this was true when covariate-by-ACB interaction terms were included; none of the interaction terms were statistically significant (all $p > .2$). Significant association was found between ACB score and individuals with cognitive frailty, as measured with TMT-A ($p = .007$) and TMT-B ($p < .001$) with model fit McFadden pseudo-R^2 for TMT-A (0.46) and TMT-B (0.47). Logistic regression results for cognitive impairment and cognitive frailty measured with TMT are shown in Table 3.

Population Prediction Model

Results from the population predictive model are ranked by gain, which is a metric based on each feature's contribution in the model. When comparing top features to other features in the model, the greater the gain the more important the feature is for prediction of the outcome. Anticholinergic burden was the top 4% predictor out of 105, 14% of 101, and 70% of 93 selected features during the classifier build, with AUCs ranging from 0.81 to 0.88 for the outcome's frailty, cognitive frailty, and cognitive impairment, respectively. Important biological and genomic markers in the predictive model may provide a better understanding to pharmacodynamic and pharmacogenomic differences effecting drug metabolism and excretion for older adults. Neuroinflammatory markers were found to be elevated coupled with decreased renal and liver function in individuals with cognitive impairment, frailty and cognitive frailty. ACB drugs are primarily metabolized in the liver by cytochrome P450 enzymes (CYP450) and are paradoxically proinflammatory (44). Neuroinflammation induced by ACB drugs increases blood–brain barrier permeability and can worsen cognitive function in older adults (9).

Discussion

Participants for all phenotypes were older with a greater proportion of females; few completed a high school education. Participants with cognitive impairment, frailty, and cognitive frailty took more medications than individuals without these phenotypes. There were smaller numbers of participants with an ACB score > 4 with most scores above zero clustered between 1 and 4; suggesting that an ACB score of 1–4 range is sufficient to show association. Logistic and ordinal regression results found in this study continues to support a relationship between anticholinergic burden and cognitive impairment, further strengthen the association with physical frailty, and provides new evidence for an association with individuals presenting with cognitive frailty.

Predictive model results provide a systems biology approach to understanding the relationship between anticholinergic burden, neuroinflammation, and impaired drug elimination. The findings from this study provide the first evidence for a relationship between anticholinergic burden and individuals with both cognitive impairment and physical frailty, affecting cognitive speed, attention, and executive functioning. The study results show a relationship between anticholinergic burden and cognitive impairment when measured with the MMSE, but no relationship was observed when cognitive impairment was measured with the TMT-A and TMT-B unless physical frailty was present. Another study found lower executive function composite scores on the Wechsler Memory Scale-Revised, Logical Memory Immediate Recall, and TMT-B test in a small sample ($n = 402$) of individuals taking anticholinergic medications over 1 year with additional findings of increased brain atrophy and clinical decline (45). Additionally, previous studies have shown a relationship between anticholinergic burden and transitions between frailty states and increased mortality for individuals who were robust at baseline; with every unit increase in burden being associated with a 73% risk of transition from robust to prefrail (46). Further these studies showed that anticholinergic burden is associated with poor mobility, functional decline, psychomotor slowing, and falls (4,20,46).

A limitation of the study is that this was a cross-sectional secondary analysis of existing data. As such, the medications are from an international database, represent a specific population of individuals, and do not consider potential differences in prescribing patterns throughout the world; generalizability may be limited to other populations. The Anticholinergic Burden Scale does not include medication dose or duration therefore, this study does not account for dose and central nervous system distribution of drugs. Drug-specific age-related pharmacodynamic changes are not well understood and further work is needed to precisely understand drug metabolism differences in older adults specifically, central and peripheral nervous system effects. Additionally, confounding may be a factor; for which it becomes difficult to distinguish between the effects of medications and disease process. Therefore, further research with adequately powered randomized controlled trials or prospective cohort studies with longitudinal follow-up periods using methods to measure ACB change in the clinical setting is needed to distinguish medication effect from disease progression.

Future research should focus on methods for detecting high risk individuals in the clinical setting, understanding mechanistic causes such as the relationship between genetic factors and anticholinergic medications as an epigenetic risk factor. Additional measures to calculate changes in anticholinergic drug exposure over time and incident cognitive impairment are needed to identify whether anticholinergic medications are a modifiable risk factor for the prevention of cognitive and physical impairment. Additionally, peripheral nervous system effects of anticholinergic drug exposure associated with frailty and cognitive frailty needs further evaluation. Confirmation of this association can be done by conducting a sensitivity analysis using more than one of the ACB tools available in a different cohort population. These findings encourage new research that may lead to effective interventions for the prevention and treatment of cognitive and physical decline. Advancing the science in understanding the mechanistic underpinnings for ACB-induced cognitive impairment and physical frailty in the clinical setting will help guide clinicians' using medications with anticholinergic effects to treat many chronic diseases, such as congestive heart failure, hypertension, and depression.

Table 1. Characteristics of Participants by Phenotype

	Cognitive Impairment (MMSE)	Frailty (CHS)	Cognitive Frailty (MMSE)	Cognitive Impairment (TMT-A)	Cognitive Impairment (TMT-B)	Cognitive Frailty (TMT-A)	Cognitive Frailty (TMT-B)
Phenotype (*n*)	(*n* = 369)	(*n* = 595)	(*n* = 257)	(*n* = 525)	(*n* = 634)	(*n* = 302)	(*n* = 325)
Age, mean (*SD*)	80 (8.7)	78 (7.9)	82 (7.4)	76 (7.7)	72 (9.0)	78 (7.4)	76 (6.9)
Gender, %							
Male (*n*)	24.0 (120)	42.8 (214)	31.9 (82)	37.1 (195)	41.9 (266)	35.1 (106)	36.0 (117)
Female (*n*)	37.6 (249)	58.2 (381)	68.1 (175)	62.9 (330)	58.0 (368)	64.9 (196)	64.0 (208)
Education, %							
No Education	56.9 (210)	39.3 (234)	58.8 (151)	42.3 (222)	25.4 (161)	46.4 (140)	30.8 (100)
Elementary Secondary	39.6 (146)	52.4 (312)	37.7 (97)	53.1 (279)	66.2 (420)	49.3 (149)	61.5 (200)
≧ High School	1.4 (5)	7.1 (42)	1.9 (5)	3.2 (17)	7.6 (48)	3.3 (10)	7.4 (24)
Medication use							
Number of medications							
0	73	83	34	107	141	35	51
1–4	228	305	169	334	408	201	208
5–7	56	100	45	70	73	53	56
≧8	12	23	9	14	12	13	10
Mean (*SD*)							
Control	2.18 (2.01)	1.75 (1.76)	2.15 (2.02)	1.95 (1.87)	1.77 (1.73)	1.85 (1.82)	1.68 (1.66)
Phenotype	2.69 (2.19)	2.89 (2.21)	3.00 (2.16)	2.44 (2.12)	2.23 (2.02)	3.01 (2.20)	2.79 (2.19)
p-value*	<.001	<.001	<.001	<.001	<.006	<.001	<.001

Note: CHS = Cardiovascular Heart Study; MMSE = Mini-Mental State Examination; SD = Standard deviation.
*Two-tailed *t* test with means and *SD*.

Table 2. Distribution of Anticholinergic Burden Score by Phenotype and Difference Between Healthy Control and Phenotype

% (*n*)	Cognitive Impairment	Frailty	Cognitive Frailty	Cognitive Impairment		Cognitive Frailty	
ACB	MMSE (*n* = 298)	CHS (*n* = 512)	MMSE (*n* = 223)	Trail A (*n* = 418)	Trail B (*n* = 493)	Trail A (*n* = 267)	Trail B (*n* = 274)
0	47.0% (141)	51.0% (261)	42.2% (94)	57.9% (242)	62.9% (310)	50.2% (134)	55.5% (152)
1	23.6% (70)	22.9% (117)	25.1% (56)	20.6% (86)	20.1% (99)	22.5% (60)	21.2% (58)
2	14.5% (43)	11.9% (61)	16.1% (36)	10.8% (45)	7.9% (39)	13.1% (35)	9.9% (27)
3	10.1% (30)	8.8% (45)	11.2% (25)	6.7% (28)	5.5% (27)	8.2% (22)	7.7% (21)
4	2.7% (8)	3% (16)	3.1% (7)	2.4% (10)	2.4% (12)	3.4% (9)	3.6% (10)
5	1.0% (3)	1.4% (7)	0.9% (2)	1.0% (4)	1.0% (5)	1.5% (4)	1.8% (5)
6	0.7% (2)	0.8% (4)	0.9% (2)	0.5% (2)	0.2% (1)	0.7% (2)	0.4% (1)
9	0.3% (1)	0.2% (1)	0.4% (1)	0.2% (1)	(0)	0.4% (1)	(0)
Control	0[6]	0[5]	0[6]	0[5]	0[4]	0[5]	0[4]
Phenotype	1[9]	0[9]	1[9]	0[9]	0[6]	0[9]	0[6]
p-value*	<.001	<.001	<.001	<.001	.042	<.001	<.001

Note: ACB = Anticholinergic drug burden; CHS = Cardiovascular Heart Study; MMSE = Mini-Mental State Examination.
*Nonparametric Kruskal–Wallis *t* test to assess differences among groups; median and maximum quantiles.

Table 3. Generalized Linear Regression Results: Association with Anticholinergic Burden and Phenotypes Versus Healthy Controls

Phenotype	(*n*)	Beta Coef	*SE*	Odds Ratio	95% CI	*p*-value
Cognitive Impairment (MMSE)	375	0.21	0.07	1.24	0.08–0.36	.002
Frailty (CHS)	595	0.31	0.07	1.36	0.17–0.45	<.001
Cognitive Frailty (MMSE)	257	0.26	0.08	1.29	0.11–0.41	<.001
Cognitive Impairment (Trail A)	545	0.20	0.14	1.22	0.14-0.11	.14
Cognitive Impairment (Trail B)	703	0.21	0.14	1.23	0.10–0.47	.12
Cognitive Frailty (Trail A)	302	0.27	0.08	1.31	0.11–0.43	<.001
Cognitive Frailty (Trail B)	325	0.38	0.09	1.46	0.19–0.57	<.001

Note: Odds ratio equals the factor by which the predicted odds change when ACB increases by 1 unit.
CHS = Cardiovascular Heart Study; CI = Confidence interval; MMSE = Mini-Mental State Examination.

Table 4. Ordinal Regression Results: Association with Anticholinergic Burden and Phenotype Versus Healthy Controls

Models	Phenotypes (MMSE and CHS)					(*n*)
1	**Cognition**					
	Moderate Cognitive Impairment					501
	Severe Cognitive Impairment					101
2	**Frailty**					
	Frail					88
	Prefrail					507
3	**Cognitive Frailty**					
	Moderate Cognitive Impairment and Frail					55
	Moderate Cognitive Impairment and Prefrail					217
	Severe Cognitive Impairment and Frail					11
	Severe Cognitive Impairment and Prefrail					76
Models	Phenotype	Beta Coef	*SE*	Odds Ratio	95% CI	*p*-value
1	Cognitive Impairment	0.19	0.07	1.21	1.07–1.37	<.001
2	Frailty	0.29	0.06	1.33	1.87–1.50	<.001
3	Cognitive Frailty	0.31	0.06	1.36	1.21–1.54	<.001

CHS = Cardiovascular Heart Study; CI = Confidence interval; MMSE = Mini-Mental State Examination.

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Conflict of Interest

L.F. serves on the editorial board of the Journals of Gerontology: Medical Sciences. There are no other conflicts of interest to declare.

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