Journal of Integrative Neuroscience

J. Integr. Neurosci. **2026**; 25(7): 51135
https://doi.org/10.31083/JIN51135

Original Research

Anticholinergic Burden and Cognitive Function, Depressive Symptoms, and Functional Performance in Individuals With Neurocognitive Disorders: Real-World Evidence

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Academic Editors: Drozdstoy Stoyanov and Bettina Platt
Submitted: 21 February 2026 Revised: 18 May 2026 Accepted: 25 May 2026 Published: 30 July 2026

Abstract

Background: Despite their negative effects on cognitive function and cognitive decline risk, drugs with anticholinergic properties are commonly prescribed, particularly in older individuals. In this observational study we aimed to shed light on the relationships between anticholinergic burden (ACB) and depressive symptoms and cognitive and functional performance in a real-world clinical setting. **Methods:** The study included individuals seeking care at the old-age psychiatry outpatient clinic of Patras University Mental Health Services. Depressive symptoms were assessed using the 15-item Geriatric Depression Scale; cognitive function was tapped using the Cognitive Telephone Screening Instrument, the Montreal Cognitive Assessment, and the Mini-Mental State Examination; and functional performance was assessed using the Bristol Activities of Daily Living Scale. Differences in demographic and clinical variables across the four diagnostic groups were analyzed. Regression analyses were performed to examine the associations between ACB, cognitive and non-cognitive symptoms, and demographic variables. In addition, clustering analyses were conducted to identify distinct, naturally occurring examinee subgroups and to assess if ACB differed across them. **Results:** The study sample consisted of individuals without cognitive impairment (N = 301), people with mild neurocognitive disorder (MiND, N = 264), major neurocognitive disorder caused by Alzheimer's disease (ADMaND, N = 114), or other diseases (nonADMaND, N = 63). Significant associations were detected between ACB and depressive symptoms (0.72, $p < 0.001$), short-term memory (–0.11, $p = 0.017$), long-term memory (–0.24, $p < 0.001$), working memory (–0.24, $p = 0.001$), attention/concentration (–0.13, $p = 0.004$), verbal fluency (–0.57, $p = 0.003$), inductive reasoning (–0.17, $p = 0.002$), basic activities of daily living (0.29, $p = 0.001$), and instrumental activities of daily living (0.58, $p < 0.001$). The clustering analyses indicated that in the cluster including individuals with more advanced cognitive decline, poorer functional status, and more severe depressive symptoms, ACB was higher compared with the second group identified by the analyses ($p < 0.001$). **Conclusions:** ACB is related to different aspects of the clinical phenotype of cognitive decline. Despite the lack of solid evidence regarding causal relationships and need for further research, minimizing ACB in clinical settings may embody a potential pragmatic strategy in managing cognitive decline in ageing.

Keywords: dementia; mild neurocognitive disorder; behavioral symptoms; activities of daily living

1. Introduction

Neurocognitive disorders are common clinical phenotypes in ageing [1]. Major neurocognitive disorder (MaND) is phenotypically characterized by progressive cognitive and functional decline, as well as neuropsychiatric symptoms like depressive symptoms [2]. Functional decline is of paramount importance for distinguishing between MaND and mild neurocognitive disorder (MiND), representing a borderline between normal ageing and early MaND. Alongside neuropsychiatric symptoms, this decline serves as the primary driver of caregiver burden [2]. Neurocognitive disorders pose one of the greatest challenges to global public health [3]. Despite this alarming trend, no widely available causal therapies currently exist. Interestingly, approx-

imately 45% of MaND cases are potentially preventable through addressing modifiable risk factors, such as lifestyle, physical, and mental health factors and also medication optimization [4]. Furthermore, clinically significant depressive symptoms affect more than 10–15% of adults aged 55 years or older, while other studies estimate the average prevalence of late-life depression to be as high as 31.74%, with rates reaching up to 40.78% in low- and middle-income countries [5,6,7]. Notably, the severity of depressive symptoms correlates positively with the progression of cognitive and functional impairment [6]. Major risk factors of depression in older adults include factors such as chronic pain, stress, social isolation and comorbidities. Among these comorbid conditions, many are managed with medications that have anticholinergic properties.

The broad group of drugs blocking the neurotransmitter acetylcholine in the central and peripheral nervous system includes some antihistamines, antidepressants, and medications for gastrointestinal and bladder disorders [8]. Even though it is well accepted that drugs with anticholinergic properties should be avoided, as outlined for instance in the American Geriatrics Society Updated Beers Criteria, the STOPP/START criteria, which are based on the Screening Tool of Older Persons' Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START) or the German PRISCUS list [9], 20–50% of older adults are exposed to anticholinergics [8]. Due to age-related changes in pharmacokinetic and pharmacodynamic effects, decreased acetylcholine-mediated transmission in the brain, and increased permeability of the blood-brain barrier, older adults are more sensitive to anticholinergic side effects [10]. Due to the widespread distribution of cholinergic receptors across the central and peripheral nervous system, their blockade can lead to a broad range of adverse effects, including peripheral symptoms (e.g., dry mouth, urinary retention, constipation, blurred vision) and central effects (e.g., confusion, attention deficits, memory impairment) [8]. When multiple drugs with anticholinergic activity are used simultaneously, their effects are cumulative, a phenomenon described as the individual's anticholinergic burden (ACB) [11]. A higher ACB is associated with poorer cognitive outcomes, increased risk of falls, delirium and all-cause mortality in older adults [8,11]. Of note, among people presenting memory complaints, one-third are on anticholinergic drugs, and those exposed to such agents demonstrate greater cognitive impairment with a clear dose–response relationship with the risk of all-cause MaND and Alzheimer's disease (AD) [12], while in older adults, exposure to anticholinergics is related to depressive symptoms [13,14]. Interestingly, reducing the anticholinergic medication load has been shown to alleviate behavioral and psychological symptoms in people with MaND and to ease care partner burden [15].

These findings indicate a relationship between ACB and cognitive decline and depressive symptoms. However, few studies have specifically examined the association between ACB and depressive symptoms and performance on basic and instrumental activities of daily living (BADL and IADL) in individuals with neurocognitive disorders [16], even though neuropsychiatric symptoms and functional decline are core components of the clinical phenotype of neurocognitive disorders. Moreover, most previous studies shedding light on the relationship between ACB and cognitive function in naturalistic settings were not based on a thorough assessment of different cognitive domains, but the cognitive assessment was restricted to brief tools like the Mini-Mental State Examination (MMSE) [9,17]. Based on real-world data, this observational study aimed to investigate the association between ACB and many aspects of the clinical phenotype of neurocognitive disorders, mainly depressive symptoms, cognitive function, and performance on BADL and IADL in users of university-based, outpatient old-age mental health services. We hypothesized that higher ACB would relate to lower performance on cognitive tasks, BADLs, and IADLs, as well as more depressive symptoms.

2. Materials and Methods

2.1 Participants

The study encompassed adults who sought old-age mental and cognitive healthcare because of cognitive complaints or as a cognitive decline prevention measure between 2017 and 2024 at the old-age psychiatry outpatient clinic of Patras University Mental Health Services. All participants or their authorized representatives provided written informed consent after a thorough description of the study aims and protocol, and prior to study enrolment. Inclusion criteria for the entire sample were (1) (self-) referral for diagnostic evaluation due to cognitive concerns, (2) age $\geq$18 years, and (3) diagnosis of MiND or MaND or absence of cognitive impairment. Exclusion criteria were (1) mental or neurological disorder or unstable medical condition potentially affecting cognitive function (e.g., major depression, schizophrenia, multiple sclerosis, seizure disorder, head injury, uncontrolled hypothyroidism), (2) hearing or visual difficulties, being potential sources of bias in diagnostic accuracy, (3) insufficient knowledge of the Greek language, and (4) unwillingness to participate in the study.

All participants underwent a thorough diagnostic work-up including a history from the examinee and from an informant; neurological and psychiatric examination; laboratory screening and brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) and assessment of cognitive function, depressive symptoms and performance of BADL and IADL [18]. The diagnosis of MiND, MaND due to AD (major neurocognitive disorder caused by Alzheimer's disease, ADMaND) and MaND due to other causes (nonADMaND) was based on international diagnostic criteria [6,19]. Individuals without cognitive impairment had no evidence of cognitive deficits, functional

impairment, or mental or neurological disorders potentially affecting cognitive function. Four clinical groups, i.e., MiND, ADMaND, nonADMaND and individuals without cognitive impairment, were considered in the analyses.

2.2 Assessment of Cognitive Function, Performance on BADL, IADL and Depressive Symptoms

Cognitive function was studied with the Cognitive Telephone Screening Instrument (COGTEL), the Serial Seven Test (SST), the MMSE and the Montreal Cognitive Assessment (MoCA), while functional performance was assessed with the Bristol ADL Scale (BADLS). Depressive symptoms were tapped with the Geriatric Depression Scale-15 (GDS) [20,21,22]. COGTEL is a brief test battery. It assesses prospective memory, i.e., the memory for intentions (0 or 1 point), verbal short- and long-term memory (0–8 points each), working memory (0–12 points), which refers to mechanisms and processes that hold the mental representations currently most needed for an ongoing cognitive task available for processing, verbal fluency (0 to unlimited; as many words as the participant can name within 1 min) and inductive reasoning (0–8 points), which is defined as 'reasoning' from particular cases to general principles. The scores of the six subtests are combined in the form of a weighted total score (7.2 × prospective memory + 1.0 × verbal short-term memory + 0.9 × verbal long-term memory + 0.8 × working memory + 0.2 × verbal fluency + 1.7 × inductive reasoning score). The SST was employed to measure auditory attention/concentration, mental tracking and computation [23]. Both MMSE and MoCA are widely used, valid brief cognitive instruments to detect cognitive impairment [24,25]. COGTEL total score and subtest scores, reflecting global cognitive function and performance on specific cognitive domains, respectively, were considered in the analyses. BADLS is a 20-item instrument capturing IADL (7 items), self-care (6 items), orientation (5 items), and mobility (2 items) [26]. Furthermore, GDS is a brief instrument for screening, evaluating and diagnosing depressive symptoms and its items require a yes/no response [21]. Of note, GDS-15 does not include items related to the somatic symptoms of depression, which could be present in older people even in the absence of depression and subsequently embody a source of bias [27].

2.3 Anticholinergic Burden Calculation

Based on data collected from medical interviews with the examinee, the informant, from the examinee's medical records, and the national electronic prescription service, the total ACB was calculated using the ACB score for German prescribers [28]. The medication list from the initial assessment was used to derive the calculated ACB. The ACB score assigns a value from 0 (no effect) to 3 (strong effect) for each drug, and the total score is the cumulative sum of their individual drug scores. Zero points are assigned to drugs with no anticholinergic effect. One or two points are assigned to drugs with weak or moderate anticholinergic effect, respectively, three points are assigned to agents with strong anticholinergic effect.

2.4 Statistical Analysis

The normality of data distribution was assessed using the Shapiro–Wilk test. Differences in demographic and clinical variables across the four diagnostic groups were analyzed using Pearson's chi-square test for categorical variables and the non-parametric Kruskal–Wallis test for continuous variables, due to deviations from normality. Post hoc analyses were conducted to examine specific pairwise differences between groups: Fisher's exact test with Bonferroni correction was applied for categorical variables, and Dunn's test with Bonferroni correction for continuous variables. The results of Dunn's test indicate both the direction and magnitude of differences between diagnostic groups. In addition, false discovery rate (FDR) correction using the Benjamini–Hochberg procedure was applied where appropriate to account for multiple testing. Effect sizes were also reported to quantify the magnitude of group differences: epsilon squared for Kruskal–Wallis tests, rank-biserial correlation for Dunn's post hoc comparisons, Cramér's V for Pearson's chi-square tests, and odds ratios for Fisher's exact tests where estimable. Missing data in the dataset were handled using two different approaches: listwise deletion and multiple imputation via the MICE algorithm (Multiple Imputation by Chained Equations). Overall, 55 participants (7.41% of the sample) had at least one missing value, corresponding to 135 observations (0.96% of all data points) across the study variables (Table 1). Both methods yielded comparable results, ensuring robustness and reliability in the subsequent analyses. Stepwise linear regression models with variable selection based on the Akaike Information Criterion (AIC) were employed for studying the relationship between cognitive function, performance on activities of daily living and depressive symptoms, which were included in models as dependent variables, and demographic data (age, sex, education) and ACB, which were the independent variables. In models with cognitive function and performance on ADL as dependent variable, depressive symptoms were included as independent variable. To explore the internal structure of the data and reduce dimensionality prior to clustering, Principal Component Analysis for mixed data (PCAmix) was performed, accommodating both quantitative and qualitative variables. Subsequently, to avoid arbitrary cut-offs (e.g., high versus low ACB) and better capture the sample's multidimensional heterogeneity, clustering analyses were conducted to identify distinct, naturally occurring patient subgroups, evaluating K-means, AGNES (Agglomerative Nesting), and DBSCAN (Density-Based Spatial Clustering of Applications with Noise). The STROBE checklist can be found in the **Supplementary Material**.

Table 1. Number and percentage of missing data per variable.

	Missing (N)	Missing (%)
Age	2	0.27%
Sex	0	0.00%
Education	3	0.40%
Total anticholinergic burden (ACB)	0	0.00%
Mini-Mental State Examination (MMSE)	7	0.94%
Montreal Cognitive Assessment (MoCA)	3	0.40%
Geriatric Depression Scale (GDS)	12	1.62%
Bristol Activities of Daily Living Scale (BADLS)	34	4.58%
Instrumental Activities of Daily Living (IADL)	33	4.45%
Basic Activities of Daily Living (BADL)	32	4.31%
Cognitive Telephone Screening Instrument (COGTEL)	0	0.00%
Prospective Memory	1	0.13%
Short-term Memory	1	0.13%
Long-term Memory	1	0.13%
Working Memory	1	0.13%
Verbal Fluency	1	0.13%
Inductive Reasoning	1	0.13%
Attention/concentration	4	0.54%

Note: Most variables had less than 2% missing data.

3. Results

The study cohort consisted of 301 individuals without neurocognitive disorder, 264 with MiND, 114 with ADMaND and 63 with nonADMaND who consequently sought care at the above-mentioned old-age psychiatry outpatient clinic. Table 2 summarizes the descriptive characteristics of the study sample. Additionally, the demographic and clinical characteristics and the results of pairwise comparison analyses are presented in Tables 2,3, respectively. Total ACB score significantly differed across the diagnostic groups, except for the differences between ADMaND and nonADMaND, as well as between MiND and ADMaND (Table 3). Even though depressive symptoms were more severe in people with cognitive impairment than in individuals without cognitive deficits, no such differences were detected between the three groups with cognitive impairment. As expected, performance on both ADL and cognitive function was lower in people with MiND than in cognitively healthy controls and in individuals with MaND compared to MiND. Interestingly, apart from concentration, no significant differences either in cognitive domains were detected between ADMaND and nonADMaND.

The stepwise regression analyses (AIC-based exploratory models) shed light on the relationship between ACB and depressive symptoms, cognitive function, and performance on ADL (Table 4). Sensitivity analyses using full multivariable models yielded consistent findings, supporting the robustness of the results. Total ACB score positively correlated with the severity of depressive symptoms and was inversely related to performance on MMSE, and all cognitive domains, which were studied, except for prospective memory. In addition, significant positive correlations were observed between ACB and BADLS scores, indicating inverse correlations between ACB and performance on both BADL and IADL. The magnitude of correlations reached its zenith in the models including depressive symptoms, long-term memory, performance on BADL and IADL as dependent variables. Moreover, the findings of the analyses highlight that the more severe the depressive symptoms, the lower the performance on prospective memory, working memory, inductive reasoning, verbal fluency, concentration/attention and BADL and IADL.

Clustering methods were employed as a data-driven approach to identify underlying patterns within the dataset, based on the simultaneous consideration of demographic, clinical, cognitive, and functional variables. A heatmap of variable loadings on the extracted components was generated for the multivariate imputation by chained equations (MICE)- imputed dataset (Fig. 1), facilitating interpretation of the latent structure. Agreement between clustering solutions was assessed using the Adjusted Rand Index (ARI) and Normalized Mutual Information (NMI), showing moderate concordance between K-means and AGNES (ARI = 0.52, NMI = 0.53), whereas DBSCAN demonstrated negligible agreement with both methods (ARI <0.05, NMI <0.05). AGNES was selected as the final clustering method due to its superior performance across validation metrics, hierarchical structure, and enhanced interpretability. The analysis was conducted using Euclidean distance and Ward's linkage, which yielded the highest agglomerative coefficient and the most stable solution. The optimal number of clusters was determined based on converging evidence from internal validation indices. The silhouette coefficient (0.28), Davies–Bouldin index (1.28), and Calinski–Harabasz index (364.54) indicated that a two-cluster solution provided the best balance between within-cluster cohesion and between-cluster separation. This is further supported by the heatmap of variable loadings on the extracted components (Fig. 1), which illustrates the underlying structure of the data, and the two-dimensional PCA visualization of clustered data (Fig. 2), which demonstrates a substantial albeit not perfect separation between the identified clusters. Cluster profiling was performed using descriptive statistics and group difference tests for key variables (Table 5). Of note, the clustering analyses unraveled the impact of ACB score on the shaping of the two clusters. Cluster 1 comprised younger individuals, predominantly female, with

Table 2. Demographic and Clinical characteristics by diagnosis group, with results of group comparisons.

	Diagnostic categories				Comparison
	Individuals without Cognitive Impairment (Group 1, G1)	Individuals with Mild Neurocognitive disorder (Group 2, G2)	Individuals with Major Neurocognitive disorder due to Alzheimer's disease (Group 3, G3)	Individuals with major Neurocognitive disorder due to other Causes (Group 4, G4)	G1 = G2 = G3 = G4
Number of Individuals, N	301	264	114	63	
Age, years	64.94 (±9.26) 66 [59, 71]*	72.61 (±8.22) 74 [68, 78]*	77.30 (±7.79) 79 [72, 83]*	69.25 (±13.31) 72 [63, 79]*	165.69 (**$p < 0.001$**) 0.22**
Sex: Female, N (%) (95% Confidence Interval)	223 (74.10%) (68.7, 78.9)	177 (67.05%) (61, 72.6)	66 (57.90%) (48.3, 67)	33 (52.40%) (39.5, 65)	17.25 (**$p < 0.001$**) 0.15***
Education, years	13.01 (±3.67) 13 [12, 16]*	10.04 (±4.52) 9 [6, 14]*	7.43 (±4.12) 6 [6, 11.25]*	10.05 (±4.33) 11 [6, 14]*	139.74 (**$p < 0.001$**) 0.19**
Total ACB	0.58 (±0.96) 0 [0, 1]*	1.24 (±1.44) 1 [0, 2]*	1.67 (±1.63) 1 [0, 2.75]*	1.95 (±2.00) 1 [1, 3]*	86.04 (**$p < 0.001$**) 0.11**
MMSE	29.06 (±1.09) 29 [28, 30]*	26.11 (±2.62) 27 [25, 28]*	18.82 (±4.98) 20 [16, 22]*	23.40 (±4.20) 24 [21, 27]*	481.81 (**$p < 0.001$**) 0.65**
MoCA	28.12 (±1.70) 28 [27, 30]*	22.80 (±3.34) 23 [21, 25]*	13.88 (±4.85) 14 [11, 17]*	18.46 (±5.25) 18 [15, 23]*	532.59 (**$p < 0.001$**) 0.72**
GDS	3.42 (±3.40) 2 [1, 6]*	4.90 (±4.20) 4 [1, 7]*	5.13 (±4.48) 4 [2, 7]*	4.97 (±4.12) 4 [2, 7]*	25.09 (**$p < 0.001$**) 0.03**
BADLS	0.54 (±1.68) 0 [0, 0]*	2.22 (±5.10) 0 [0, 3]*	10.55 (±12.20) 7 [2, 14]*	7.43 (±8.76) 5 [0, 13]*	228.15 (**$p < 0.001$**) 0.31**
IADL	0.46 (±1.31) 0 [0, 0]*	1.68 (±3.16) 0 [0, 2]*	7.12 (±6.56) 6 [2, 10]*	5.23 (±5.99) 3 [0, 9]*	224.56 (**$p < 0.001$**) 0.30**
BADL	0.09 (±0.63) 0 [0, 0]*	0.53 (±2.34) 0 [0, 0]*	3.10 (±5.59) 0 [0, 4]*	2.23 (±3.35) 0 [0, 4]*	145.36 (**$p < 0.001$**) 0.19**
COGTEL	32.61 (±8.89) 32.90 [26.5, 39.10]*	16.93 (±6.19) 16.85 [12.70, 21.05]*	7.86 (±4.77) 7.35 [4.53, 11.18]*	12.57 (±9.37) 10.40 [5.70, 16.60]*	482.72 (**$p < 0.001$**) 0.65**
Prospective Memory	0.50 (±0.50) 0 [0, 1]*	0.04 (±0.20) 0 [0, 0]*	0.00 (±0.00) 0 [0, 0]*	0.08 (±0.27) 0 [0, 0]*	218.51 (**$p < 0.001$**) 0.29**
Short-term Memory	5.11 (±1.48) 5 [4, 6]*	3.35 (±1.44) 3 [2, 4]*	1.64 (±1.32) 2 [0, 3]*	2.17 (±1.68) 2 [1, 3]*	334.02 (**$p < 0.001$**) 0.45**
Long-term Memory	6.47 (±1.42) 7 [6, 8]*	4.05 (±1.82) 4 [3, 5]*	1.87 (±1.43) 2 [0.25, 3]*	2.87 (±1.92) 3 [2, 4]*	397.95 (**$p < 0.001$**) 0.54**
Working Memory	8.11 (±2.50) 8 [6, 10]*	5.26 (±2.42) 5 [4, 6]*	2.76 (±2.04) 2 [2, 4]*	3.67 (±2.43) 3 [2, 5]*	325.87 (**$p < 0.001$**) 0.44**
Verbal Fluency	21.21 (±7.51) 20 [16, 25]*	14.76 (±7.09) 14 [10, 19]*	7.65 (±5.49) 6 [4, 11]*	11.14 (±8.11) 9 [6.5, 13]*	276.55 (**$p < 0.001$**) 0.37**
Inductive Reasoning	4.31 (±2.44) 4 [2, 6]*	1.47 (±1.39) 2 [0, 2]*	0.42 (±0.82) 0 [0, 1]*	0.95 (±1.40) 0 [0, 2]*	343.43 (**$p < 0.001$**) 0.46**
Attention/concentration	4.73 (±0.92) 5 [5, 5]*	3.55 (±1.83) 5 [2, 5]*	1.56 (±1.83) 1 [0, 2]*	2.65 (±2.01) 2 [1, 5]*	246.92 (**$p < 0.001$**) 0.33**

* Mean (±Standard Deviation) Median [First Quartile, Third Quartile].

** Kruskal – Wallis test statistic adjusted for ties (false discovery rate [FDR]-adjusted *p*-value) with epsilon squared as effect size.

*** Pearson's Chi-square test statistic (FDR-adjusted *p*-value) with Cramér's V as effect size.

Bold *p*-values indicate statistically significant results at the 0.05 level.

Table 3. Pairwise comparisons of demographic and clinical characteristics across diagnostic groups.

	Pairwise comparisons					
	G1 vs G2	G1 vs G3	G1 vs G4	G2 vs G3	G2 vs G4	G3 vs G4
Age, years	–9.43 (**$p < 0.001$**) –0.35‡	–11.55 (**$p < 0.001$**) –0.42‡	–4.09 (**$p < 0.001$**) –0.15‡	–4.26 (**$p < 0.001$**) –0.16‡	1.63 ($p = 0.619$) 0.06‡	4.50 (**$p < 0.001$**) 0.17‡
Sex: Female	($p = 0.468$) 0.71‡‡	(**$p = 0.011$**) 0.48‡‡	(**$p = 0.008$**) 0.39‡‡	($p = 0.610$) 0.68‡‡	($p = 0.240$) 0.54‡‡	($p = 1.00$) 0.80‡‡
Education, years	7.74 (**$p < 0.001$**) 0.28‡	10.98 (**$p < 0.001$**) 0.40‡	4.80 (**$p < 0.001$**) 0.18‡	4.99 (**$p < 0.001$**) 0.18‡	0.09 ($p = 1.00$) 0.0‡	–3.49 (**$p = 0.003$**) –0.13‡
Total ACB	–6.14 (**$p < 0.001$**) –0.23‡	–7.28 (**$p < 0.001$**) –0.27‡	–6.53 (**$p < 0.001$**) –0.24‡	–2.53 ($p = 0.069$) –0.09‡	–2.76 (**$p = 0.035$**) –0.10‡	–0.66 ($p = 1.00$) –0.02‡
MMSE	13.65 (**$p < 0.001$**) 0.50‡	19.93 (**$p < 0.001$**) 0.74‡	11.44 (**$p < 0.001$**) 0.42‡	9.27 (**$p < 0.001$**) 0.34‡	3.24 (**$p = 0.007$**) 0.12‡	–3.64 (**$p = 0.002$**) –0.13‡
MoCA	14.86 (**$p < 0.001$**) 0.55‡	20.43 (**$p < 0.001$**) 0.75‡	12.92 (**$p < 0.001$**) 0.48‡	8.87 (**$p < 0.001$**) 0.33‡	3.81 (**$p < 0.001$**) 0.14‡	–2.94 (**$p = 0.019$**) –0.11‡
GDS	–4.24 (**$p < 0.001$**) –0.16‡	–3.63 (**$p = 0.002$**) –0.13‡	–2.82 (**$p = 0.029$**) –0.10‡	–0.37 ($p = 1.00$) –0.01‡	–0.28 ($p = 1.00$) –0.01‡	0.02 ($p = 1.00$) 0.0‡
BADLS	–6.12 (**$p < 0.001$**) –0.23‡	–13.72 (**$p < 0.001$**) –0.52‡	–9.08 (**$p < 0.001$**) –0.34‡	–9.01 (**$p < 0.001$**) –0.34‡	–5.29 (**$p < 0.001$**) –0.20‡	1.88 ($p = 0.360$) 0.07‡
IADL	–6.03 (**$p < 0.001$**) –0.23‡	–13.70 (**$p < 0.001$**) –0.51‡	–8.83 (**$p < 0.001$**) –0.33‡	–9.05 (**$p < 0.001$**) –0.34‡	–5.09 (**$p < 0.001$**) –0.19‡	2.09 ($p = 0.221$) 0.08‡
BADL	–2.43 ($p = 0.091$) –0.09‡	–9.89 (**$p < 0.001$**) –0.37‡	–8.33 (**$p < 0.001$**) –0.31‡	–7.93 (**$p < 0.001$**) –0.30‡	–6.77 (**$p < 0.001$**) –0.25‡	–0.22 ($p = 1.00$) –0.01‡
COGTEL	14.73 (**$p < 0.001$**) 0.54‡	19.24 (**$p < 0.001$**) 0.71‡	12.22 (**$p < 0.001$**) 0.45‡	7.80 (**$p < 0.001$**) 0.29‡	3.22 (**$p = 0.008$**) 0.12‡	–2.70 (**$p = 0.042$**) –0.10‡
Prospective Memory	12.90 (**$p < 0.001$**) 0.47‡	10.81 (**$p < 0.001$**) 0.40‡	7.21 (**$p < 0.001$**) 0.26‡	0.90 ($p = 1.00$) 0.03‡	–0.64 ($p = 1.00$) –0.02‡	–1.21 ($p = 1.00$) –0.04‡
Short-term Memory	11.08 (**$p < 0.001$**) 0.41‡	16.19 (**$p < 0.001$**) 0.59‡	10.80 (**$p < 0.001$**) 0.40‡	7.54 (**$p < 0.001$**) 0.28‡	4.00 (**$p < 0.001$**) 0.15‡	–1.81 ($p = 0.421$) –0.07‡
Long-term Memory	12.83 (**$p < 0.001$**) 0.47‡	17.68 (**$p < 0.001$**) 0.65‡	11.17 (**$p < 0.001$**) 0.41‡	7.68 (**$p < 0.001$**) 0.28‡	3.31 (**$p = 0.006$**) 0.12‡	–2.53 ($p = 0.069$) –0.09‡
Working Memory	10.94 (**$p < 0.001$**) 0.40‡	16.02 (**$p < 0.001$**) 0.59‡	10.59 (**$p < 0.001$**) 0.39‡	7.48 (**$p < 0.001$**) 0.27‡	3.88 (**$p = 0.001$**) 0.14‡	–1.88 ($p = 0.362$) –0.07‡
Verbal Fluency	9.15 (**$p < 0.001$**) 0.34‡	15.18 (**$p < 0.001$**) 0.56‡	9.42 (**$p < 0.001$**) 0.35‡	8.00 (**$p < 0.001$**) 0.29‡	3.80 (**$p = 0.001$**) 0.14‡	–2.33 ($p = 0.121$) –0.09‡
Inductive Reasoning	13.05 (**$p < 0.001$**) 0.48‡	15.84 (**$p < 0.001$**) 0.58‡	10.40 (**$p < 0.001$**) 0.38‡	5.71 (**$p < 0.001$**) 0.21‡	2.42 ($p = 0.094$) 0.09‡	–1.92 ($p = 0.331$) –0.07‡
Concentration / Attention	7.84 (**$p < 0.001$**) 0.29‡	14.86 (**$p < 0.001$**) 0.55‡	7.93 (**$p < 0.001$**) 0.29‡	8.72 (**$p < 0.001$**) 0.32‡	3.12 (**$p = 0.011$**) 0.11‡	–3.47 (**$p = 0.003$**) –0.13‡

G1: Individuals without Cognitive Impairment; G2: Individuals with Mild Neurocognitive Disorder; G3: Individuals with Major Neurocognitive disorder due to Alzheimer's disease; G4: Individuals with Major Neurocognitive disorder due to other Causes.

‡ Dunn's test statistic with Bonferroni correction (*p*-value) with rank-biserial correlation as effect size.

‡‡ (*p*-value from Fisher's exact test with Bonferroni correction) odds ratio is estimated as effect size.

Bold *p*-values indicate statistically significant results at the 0.05 level.

Table 4. Stepwise regression results showing the coefficients (Estimates) and significance levels (*p*-values) for each dependent variable.

	MMSE	GDS	Prospective memory	Short-term memory	Long-term memory	Working memory
Sex: Female	0.79 (0.08) **(*p* = 0.012)** (0.19, 1.39)*	1.56 (0.18) **(*p* < 0.001)** (0.98, 2.14)*	0.06 (0.07) **(*p* = 0.046)** (0.0, 0.12)*	0.54 (0.13) **(*p* < 0.001)** (0.27, 0.81)*	0.83 (0.17) **(*p* < 0.001)** (0.52, 1.15)*	
Age	−0.11 (−0.25) **(*p* < 0.001)** (−0.14, −0.08)*	−0.03 (−0.08) **(*p* = 0.033)** (−0.06, 0.0)*	−0.01 (−0.30) **(*p* < 0.001)** (−0.01, −0.01)*	−0.04 (−0.22) **(*p* < 0.001)** (−0.06, −0.03)*	−0.06 (−0.28) **(*p* < 0.001)** (−0.08, −0.05)*	−0.06 (−0.21) **(*p* < 0.001)** (−0.08, −0.04)*
Education, years	0.32 (0.32) **(*p* < 0.001)** (0.26, 0.39)*	−0.14 (−0.16) **(*p* < 0.001)** (−0.21, −0.08)*	0.02 (0.21) **(*p* < 0.001)** (0.01, 0.03)*	0.13 (0.30) **(*p* < 0.001)** (0.10, 0.16)*	0.14 (0.28) **(*p* < 0.001)** (0.11, 0.18)*	0.26 (0.37) **(*p* < 0.001)** (0.21, 0.30)*
Total ACB	−0.37 (−0.11) **(*p* = 0.001)** (−0.57, −0.16)*	0.72 (0.26) **(*p* < 0.001)** (0.53, 0.91)*	−0.01 (−0.07) (*p* = 0.057) (−0.04, 0.0)*	−0.11 (−0.08) **(*p* = 0.017)** (−0.21, −0.02)*	−0.24 (−0.14) **(*p* < 0.001)** (−0.34, −0.13)*	−0.24 (−0.11) **(*p* = 0.001)** (−0.38, −0.10)*
GDS	−0.20 (−0.17) **(*p* < 0.001)** (−0.27, −0.12)*		−0.02 (−0.11) **(*p* = 0.002)** (−0.02, 0.0)*	−0.03 (−0.07) (*p* = 0.057) (−0.07, 0.0)*	−0.04 (−0.06) (*p* = 0.056) (−0.08, 0.0)*	−0.09 (−0.12) **(*p* < 0.001)** (−0.14, −0.04)*
	R^2 = 0.31	R^2 = 0.14	R^2 = 0.22	R^2 = 0.23	R^2 = 0.30	R^2 = 0.30
	Adj. R^2 = 0.31	Adj. R^2 = 0.13	Adj. R^2 = 0.21	Adj. R^2 = 0.23	Adj. R^2 = 0.30	Adj. R^2 = 0.30
	Verbal Fluency	Inductive Reasoning	Concentration / Attention	COGTEL	Basic Activities of Daily Living	Instrumental Activities of Daily Living
Sex: Female	1.27 (0.07) **(*p* = 0.027)** (0.17, 2.37)*		−0.29 (−0.07) **(*p* = 0.033)** (−0.55, −0.03)*	1.81 (0.07) **(*p* = 0.017)** (0.36, 3.26)*		
Age	−0.16 (−0.19) **(*p* < 0.001)** (−0.21, −0.11)*	−0.05 (−0.22) **(*p* < 0.001)** (−0.07, −0.04)*	−0.03 (−0.17) **(*p* < 0.001)** (−0.04, −0.02)*	−0.35 (−0.30) **(*p* < 0.001)** (−0.42, −0.29)*	0.04 (0.12) **(*p* = 0.002)** (0.01, 0.06)*	0.05 (0.11) **(*p* = 0.002)** (0.02, 0.08)*
Education, years	0.86 (0.45) **(*p* < 0.001)** (0.74, 0.98)*	0.22 (0.41) **(*p* < 0.001)** (0.19, 0.25)*	0.14 (0.34) **(*p* < 0.001)** (0.11, 0.17)*	1.14 (0.43) **(*p* < 0.001)** (0.98, 1.30)*	0.09 (−0.13) **(*p* = 0.001)** (−0.14, −0.04)*	−0.21 (−0.21) **(*p* < 0.001)** (−0.27, −0.14)*
Total ACB	−0.57 (−0.10) **(*p* = 0.003)** (−0.94, −0.20)*	−0.17 (−0.10) **(*p* = 0.002)** (−0.28, −0.07)*	−0.13 (−0.10) **(*p* = 0.004)** (−0.22, −0.05)*	−1.08 (−0.13) **(*p* < 0.001)** (−1.57, −0.60)*	0.29 (0.13) **(*p* = 0.001)** (0.13, 0.45)*	0.58 (0.19) **(*p* < 0.001)** (0.37, 0.79)*
GDS	−0.18 (−0.08) **(*p* = 0.010)** (−0.32, −0.05)*	−0.06 (−0.10) **(*p* = 0.002)** (−0.10, −0.02)*	−0.05 (−0.11) **(*p* = 0.002)** (−0.08, −0.02)*	−0.36 (−0.12) **(*p* < 0.001)** (−0.54, −0.18)*	0.10 (0.13) **(*p* = 0.001)** (0.04, 0.16)*	0.19 (0.17) **(*p* < 0.001)** (0.11, 0.26)*
	R^2 = 0.35	R^2 = 0.34	R^2 = 0.24	R^2 = 0.44	R^2 = 0.10	R^2 = 0.19
	Adj. R^2 = 0.35	Adj. R^2 = 0.33	Adj. R^2 = 0.24	Adj. R^2 = 0.44	Adj. R^2 = 0.09	Adj. R^2 = 0.19

* Unstandardized regression coefficient (Standardized coefficient) (FDR-adjusted *p*-value) (95% Confidence Interval).

Empty cells point to variables not included in the final selected regression models.

Bold *p*-values indicate statistically significant results at the 0.05 level.

All outcomes analyzed using multiple linear regression.

higher educational attainment, mild depressive symptoms and low ACB. Cognitive performance was preserved, and daily functioning was largely maintained. Thus, Cluster 1 encompassed fewer cognitively impaired and healthier individuals. Cluster 2 included participants with lower educational attainment, higher ACB score, more pronounced depressive symptoms, lower cognitive and functional performance, who represented a clinically more advanced phenotype. Indeed, the distribution of diagnoses across clusters (Fig. 3) aligns with this phenotypic difference. Cluster 1 mainly included individuals without cognitive impairment and individuals with MiND, whereas Cluster 2 comprised a higher proportion of individuals with MiND, ADMaND and nonADMaND, confirming the meaningful differentiation between service users' groups.

4. Discussion

The present study sheds light on the impact of ACB on different aspects of the clinical phenotypes of MiND, ADMaND and nonADMaND. The study and its findings expand previous literature as they (i) show that ACB is associated with depressive symptoms, cognitive and functional performance in ageing (ii) clarify the relationship of ACB and performance on different cognitive domains based on an in-depth pragmatic cognitive assessment, and (iii) underscore the shaping impact of ACB on clinical phenotypes of people seeking care in the real-world setting of a university-based old-age psychiatry outpatient clinic, as illustrated by the results of the clustering analyses.

Depressive symptoms were shown to be significantly correlated with ACB. This observation is in line with past reports, which pointed out that high ACB scores are related to more depressive symptoms in community-dwelling older adults [14,29]. In particular, ACB was independently related to depressive symptoms in a sample of older African-Americans with MiND who were enrolled in a clinical trial [29], while high anticholinergic load was found to be related to depressive symptoms in older individuals without mental disorders, sensory loss, severe or terminal illness admitted to an outpatient geriatric clinic [14]. Interestingly, ACB was related to high scores on the neuropsychiatric inventory in a rather small group of outpatients visiting a university-based memory clinic [30]. The linkage between depressive symptoms and ACB may be attributable to neurobiological mechanisms implicated in the development of depression. Mounting evidence from experimental studies indicates that an imbalance of multiple neurobiological systems underlying depression may beget cholinergic dysfunction in brain regions like hippocampus, amygdala, prefrontal cortex which may, in turn, increase proneness to cognitive dysfunction and the manifestation of depressive symptoms, or even precipitate them [31,32]. Hence, high ACB may lead to further disruption of already impaired cholinergic transmission in selected brain regions.

In our sample of consecutively recruited users of old-age psychiatry outpatient services, exposure to ACB inversely correlated with performance on memory-, verbal fluency-, inductive reasoning- and concentration/attention-tasks. These findings build on previous research endeavours, which, however, were in most cases not based on an extensive assessment of cognitive functions [9,17]. The correlation between prospective memory and ACB marginally did not pass the significance threshold. This may be a spurious finding which warrants further investigation, since the assessment of this memory aspect may not be thorough enough in COGTEL [20]. Studies with different designs (e.g., nested case-control studies, cross-sectional population-based studies, meta-analyses of observational studies) and in variable populations, as hospitalized geriatric patients, adults with no cognitive dysfunction, subjective cognitive complaints or cognitive impairment, unraveled that high ACB scores predict worse cognitive performance particularly in executive function- and episodic memory tasks and increase the risk of cognitive decline and MaND [17,33,34,35,36,37,38]. Interestingly, compared to cognitively normal older people not on medication with medium or high anticholinergic activity, reduced total cortical volume and temporal lobe cortical thickness and greater lateral ventricle and inferior ventricle volumes were detected in those treated with such medicines [39]. These changes may be explainable by anticholinergic medication exposure- related brain changes akin to those of AD, such as the formation of amyloid β plaques and neurofibrillary tangles, which exert detrimental effects on episodic memory, as anticholinergic medicines directly do through chronic anticholinergic depletion [37]. In addition, since ACB increases the risk of vascular MaND, vascular and inflammatory changes may serve as mediators of the link between high ACB and cognitive dysfunction [33,37]. A vascular hypothesis could also explain the observed relationship between ACB score and executive function, since impaired executive function is a common symptom of vascular MaND [40].

Exposure to anticholinergic agents may affect diagnostic classification. Except for the association between ACB score and both depressive symptoms, being a common neuropsychiatric symptom in MiND and MaND, and cognitive dysfunction, close relationships were observed between ACB and performance on BADL and IADL in our clinical cohort. To our knowledge, such a linkage has not been thoroughly studied yet. Considering the important role of functional performance in diagnosing MaND and distinguishing between MiND and MaND, the influence of ACB burden on establishing clinical diagnoses becomes evident [41]. Indeed, this influence is highlighted through the significant difference in total ACB scores between the two clinical patterns identified by the cluster analysis, being an unsupervised, data-driven approach that does not rely on arbitrary cut-off values for categorization. Higher

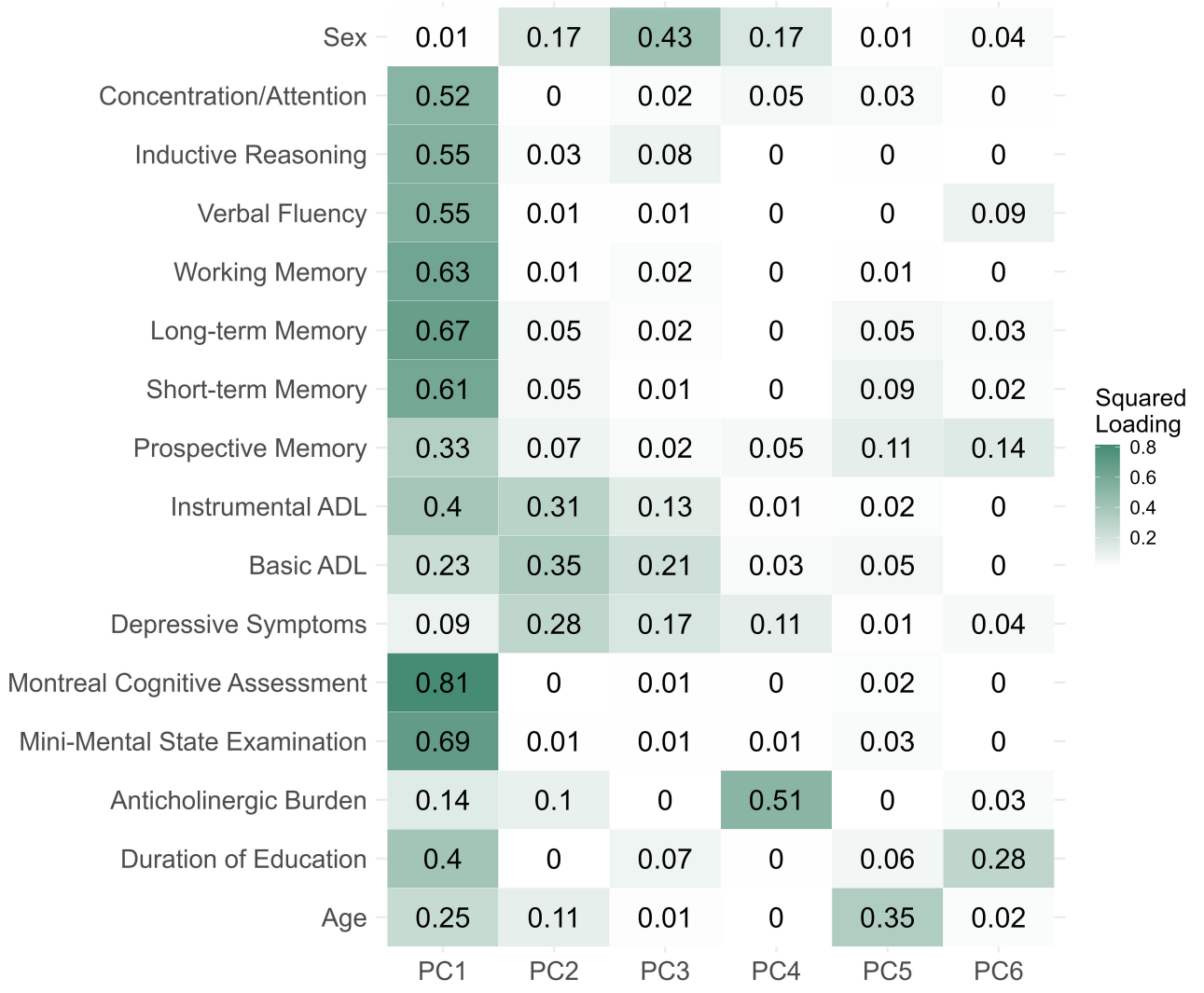

Fig. 1. Heatmap of variable loadings on the extracted components.

ACB scores characterized the cluster including people in more advanced stages of cognitive decline and lower functional performance. Their MoCA- and MMSE scores are compatible with MaND or MiND at the border to MaND, while performance on MoCA and/or MMSE of individuals included in the other cluster point to normal cognition or early stages of MiND [24,25]. In accordance with this line of thought, there was a clear difference in the distribution of diagnoses across clusters (Fig. 3) with Cluster 2 comprising a higher proportion of individuals with MiND, ADMaND and nonADMaND, and Cluster 1 mainly encompassing individuals without cognitive impairment and individuals with MiND. Nonetheless, the difference in ACB between MiND and ADMaND was with a p value of 0.07 marginally not significant, possibly pointing to the blurred boundaries between MiND and ADMaND and the presence of a grey zone between the two diagnostic entities in clinical contexts, despite the detailed diagnostic work-up [42].

Since ACB is linked to all three main pillars of symptoms of MaND, careful weighting of known anticholinergic medication risks vs. benefits should be applied in users seeking care at old-age psychiatry outpatient clinics or memory clinics and deprescribing opportunities should be implemented whenever possible [43]. Of note, the average ACB scores in all diagnostic categories included in our study point to a low risk of anticholinergic effects (ACB <3) [30]. Thus, even low ACB affects cognitive function, the manifestation of depressive symptoms, and performance on ADL in this population. Therefore, minimizing ACB by opting for alternatives with similar therapeutic effects but devoid of anticholinergic properties should be considered in shared decision-making [44]. Effectiveness should be the first consideration when choosing for instance, an antidepressant or an antipsychotic agent. However, medicines of the same subclass may be equally effective, while they significantly differ in their anticholinergic properties [45]. Thus, based on a careful weighing up of the risks and bene-

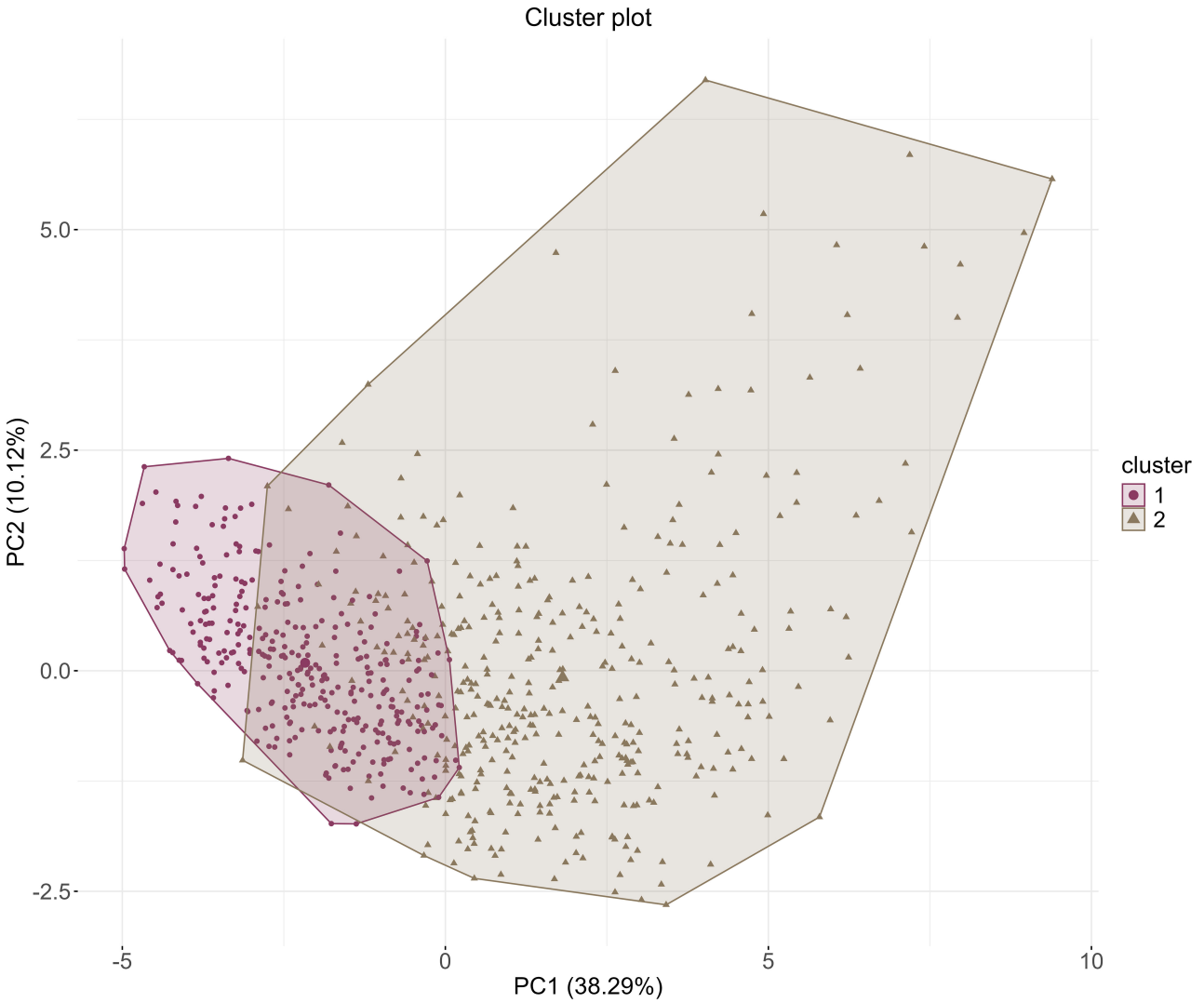

Fig. 2. Two-Dimensional PCA visualization of clustered data. PCA, Principal Component Analysis.

fits, prioritizing equally effective medicines with lower anticholinergic properties over those with higher ACB may be a pragmatic strategy, following the principles of precision medicine and values-based practice [46], to reduce ACB and its effects on clinical phenotypes and cognitive decline risk. Moreover, the exploration of the potential of non-pharmacological interventions prior to deciding on a medicine based on the needs of each person with cognitive impairment or other diseases, could also contribute to avoiding an increase in ACB as well as drug side-effects, particularly in the light of the high effectiveness of such interventions [47].

The detected differences in clinical characteristics and the relationship between depressive symptoms and cognitive function in our sample are concordant with observations of previous reports. In line with findings from the Greek epidemiological study Hellenic Longitudinal Investigation of Aging and Diet (HELIAD), more depressive symptoms were detected in the three groups with cognitive impairment compared to individuals without cognitive decline [6]. In our sample, ACB score was higher in people with cognitive impairment than in the cognitively normal group. This observation is also in line with past reports, highlighting that anticholinergic exposure is higher in MaND than in cognitively healthy ageing [48]. Moreover, the significantly higher concentration/attention of individuals with nonADMaND in comparison to ADMaND and the lack of further differences in cognitive function between the two groups should be treated with caution, considering the inhomogeneous character of the nonADMaND group, including different cognitive phenotypes classified (MaND with Lewy bodies, vascular MaND, frontotemporal lobar degeneration, normal pressure hydrocephalus, posterior cortical atrophy). Interestingly, performance on IADL differed between cognitively healthy participants and MiND, while BADL did not. Indeed, MiND is characterized by mild decline in IADL but not in BADL [49,50]. Moreover, the close, inverse relationship between depres-

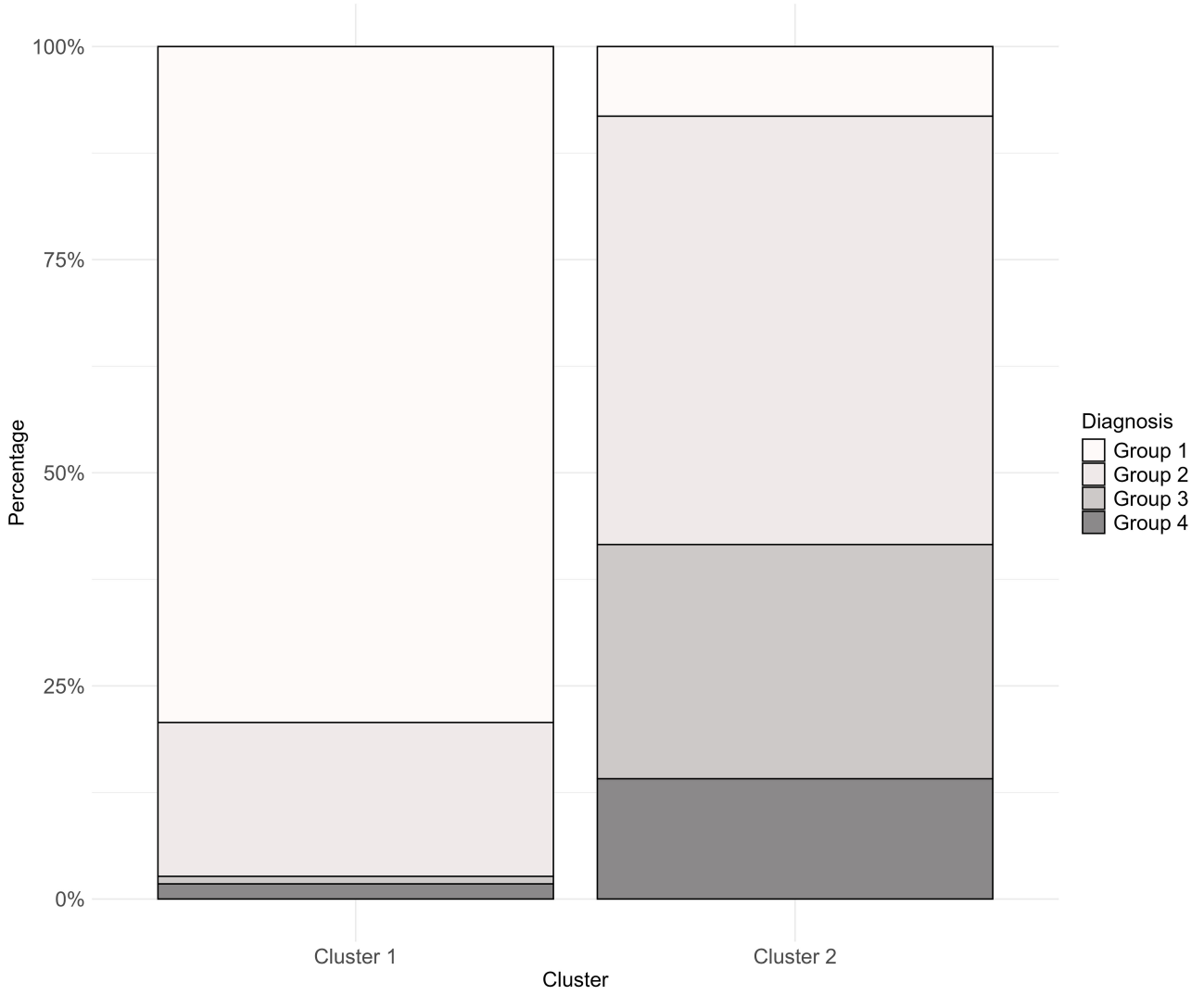

Fig. 3. Distribution of diagnoses across clusters.

sive symptoms and performance on different cognitive domains, but not on short- and long-term verbal memory, points to the close, but complex linkages between depressive symptoms and cognitive function in ageing. Depressive symptoms may embody a risk factor for cognitive decline or even MaND, or form symptoms of prodromal MaND [51].

This study has several limitations. First, the cross-sectional study design does not enable the identification of presumed causal relationships. In particular, it may be assumed that high ACB contributes to more severe depressive or other neuropsychiatric symptoms, while it cannot be precluded that more severe symptoms have rendered the prescription of medications with anticholinergic properties inevitable. Since the severity of depressive symptoms in most cases did not surpass the level of high clinical significance in our study, as clearly indicated by the mean total GDS scores, and individuals with major depression were excluded from the study, it can be hypothesized that the detected correlation is not mainly driven by the therapeutic needs of examinees due to depressive or other neuropsychiatric symptoms. Nonetheless, the relatively mild depressive symptoms at the time point of the initial assessment may be attributed to the therapeutic effects of psychotropic medication. This vicious circle can be deciphered through longitudinal studies that are urgently warranted. Second, the recruitment of study participants at a single centre may undermine the generalizability of the findings. Third, in our study, it was assumed that medicines were taken as the prescriber intended, though this is commonly not the case in approximately 60% of prescribed medicines [52]. Fourth, this study did not account for medication duration or medication changes prior to the initial assessment. This is a notable limitation, as cumulative anticholinergic exposure has been linked to increased risk of cognitive impairment in older residents of nursing homes who had depression [53]. Fifth, even though the study sample was not restricted to people aged 65 or older, depressive symptoms were tapped

Table 5. Demographic and clinical characteristics of Cluster 1 and Cluster 2.

	Cluster 1	Cluster 2	*p*-value
Age, years	66.12 (±9.66) 67 [60, 73]*	73.10 (±9.57) 74 [68, 80]*	**$p < 0.001$****
Sex: Female, N (%) (95% Confidence Interval)	252 (74.60%) (69.60, 79.10)	247 (61.10%) (56.20, 65.90)	**$p < 0.001$*****
Education, years	13.25 (±3.41) 14 [12, 16]*	8.83 (±4.44) 6 [6, 12]*	**$p < 0.001$****
Total ACB	0.43 (±0.70) 0 [0, 1]*	1.65 (±1.65) 1 [0, 2]*	**$p < 0.001$****
MMSE	28.67 (±1.67) 29 [28, 30]*	23.65 (±4.99) 25 [21, 27]*	**$p < 0.001$****
MoCA	27.57 (±2.26) 28 [26, 29]*	19.55 (±5.78) 21 [16, 24]*	**$p < 0.001$****
GDS	3.00 (±2.96) 2 [1, 5]*	5.45 (±4.39) 5 [2, 8]*	**$p < 0.001$****
BADLS	0.55 (±1.64) 0 [0, 0]*	5.53 (±9.15) 2 [0, 7]*	**$p < 0.001$****
IADL	0.44 (±1.27) 0 [0, 0]*	3.81 (±5.37) 1.5 [0, 5]*	**$p < 0.001$****
BADL	0.11 (±0.67) 0 [0, 0]*	1.64 (±4.10) 0 [0, 0]*	**$p < 0.001$****
COGTEL	31.51 (±9.01) 30.55 [24.13, 38.50]*	13.18 (±7.31) 12.65 [7.50, 17.33]*	**$p < 0.001$****
Prospective Memory	0.45 (±0.50) 0 [0, 1]*	0.03 (±0.18) 0 [0, 0]*	**$p < 0.001$****
Short-term Memory	5.01 (±1.45) 5 [4, 6]*	2.60 (±1.63) 3 [2, 4]*	**$p < 0.001$****
Long-term Memory	6.30 (±1.53) 6 [5, 8]*	3.17 (±1.94) 3 [2, 4]*	**$p < 0.001$****
Working Memory	7.99 (±2.50) 8 [6, 10]*	4.14 (±2.46) 4 [2, 6]*	**$p < 0.001$****
Verbal Fluency	21.44 (±7.42) 20 [16, 25]*	11.40 (±6.77) 10 [7, 15]*	**$p < 0.001$****
Inductive Reasoning	4.03 (±2.40) 4 [2, 6]*	1.06 (±1.44) 0 [0, 2]*	**$p < 0.001$****
Concentration/Attention	4.79 (±0.79) 5 [5, 5]*	2.70 (±2.03) 2 [1, 5]*	**$p < 0.001$****

* Mean (±Standard Deviation) Median [First Quartile, Third Quartile].

** (*p*-value from Kruskal – Wallis test adjusted for ties).

*** (*p*-value from Pearson's Chi-square test).

Bold *p*-values indicate statistically significant results at the 0.05 level.

with GDS, which is a tool designed to assess depression in older adults. Nevertheless, GDS was recently shown to have good diagnostic sensitivity and specificity in detecting depressive symptoms even in adults aged 18–54 [54]. Furthermore, the study does not provide evidence on the potential benefits of deprescribing anticholinergic agents and reducing ACB. Indeed, the effects of reduction of ACB on cognitive function, neuropsychiatric symptoms and functional performance remain largely unknown [9]. Furthermore, the clinical diagnoses of MiND, ADMaND, non-ADMaND were based on international diagnostic criteria. Nevertheless, the clinical diagnoses are neither always confirmed at autopsy nor always supported by biomarker constellations typical for AD [55]. Thus, possibly erroneous clinical assessments should also be taken into account. Finally, the cognitive assessment did not include computerized testing which is superior to conventional cognitive tests for instance in terms of precision measurement of required time or reaction time [56].

5. Conclusions

In this single-centre, real-world sample of users of the services of an old-age psychiatry outpatient clinic, we found that ACB is positively associated with depressive symptoms, and inversely related to performance on different cognitive domains as well as to functional performance. Thus, the clinical significance of ACB in the diagnostic workup and management of cognitive complaints and their clinical consequences becomes evident and warrants further investigation in longitudinal and interventional multi-centre studies, so that light is shed on the potential causal effects of ACB on different aspects of the clinical phenotypes of MiND, ADMaND, nonADMaND and the potential benefits for the personalized cognitive decline risk- and/or postdiagnostic management that could arise from reducing ACB.

Availability of Data and Materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

The study design was conceptualized by PA. PA, LP, TK, PE and PF contributed to methodology. MS in collaboration with LP, CLK, EK, VPE, VPA, IM, L-MM, AK, PF, PA conducted the investigation. TK and PE performed the statistical analyses. LP, TK, CLK, EK, VPE, VPA, IM, L-MM, AK, TV, VP, PE, PF, and PA contributed to the interpretation of the findings. PA and LP wrote the first draft of the manuscript, which was critically revised by all authors. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted with informed consent from all participants and in accordance with the Declaration of Helsinki and approved by the Bioethics and Research Ethics Committee of Patras General University Hospital (approval number: 2017/10/15, and 26335/14.10.2021).

Acknowledgment

We would like to express our gratitude to Dr. Christina Petropoulou for her contribution to parts of the first draft of the manuscript.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/JIN51135.

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