Received: 13 May 2024 | Revised: 21 August 2024 | Accepted: 8 October 2024

DOI: 10.1002/dad2.70034

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

The relationship between anticholinergic burden and frailty in the year preceding a diagnosis of dementia with Lewy bodies

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Funding information
National Institute on Aging; National Institutes of Health, Grant/Award Number: R21AG074368

Abstract

INTRODUCTION: Little is known regarding the relationship between anticholinergic medications and frailty in dementia with Lewy bodies (DLB).

METHODS: Anticholinergic Cognitive Burden Scale (ACB) and Claims-based Frailty Index scores were calculated for 12 months prior to the dementia diagnosis using electronic medical record and claims data. Logistic regression was used to estimate the association between ACB and odds of frailty.

RESULTS: Compared to controls (n = 525), a diagnosis of DLB (n = 175; adjusted odds ratio [aOR]: 15.1, 95% confidence interval [CI]: 7.0–33.9) or Alzheimer's disease (AD: n = 525; aOR = 7.7, 95% CI: 4.4–13.7) was associated with an increased odds of frailty. Patients with DLB had greater prescriptions for anticholinergic medications than patients with AD ($p_B < 0.001$; 23% vs 9.7%). ACB was positively correlated with frailty for all groups ($r = 0.30$ to 0.47, $p < 0.001$).

DISCUSSION: Cumulative anticholinergic burden may be a modifiable predictor of frailty among older adults, including those newly diagnosed with dementia.

KEYWORDS
Alzheimer's disease, anticholinergic, early-stage dementia, frailty, Lewy body, mild cognitive impairment, mild dementia, polypharmacy, predementia, prodromal

Highlights

- Patients with newly diagnosed dementia with Lewy bodies (DLB) are more likely to have prescriptions for anticholinergic medications relative to patients newly diagnosed with Alzheimer's disease (AD) and older adults without documented cognitive impairment.
- In the year prior to a documented dementia diagnosis, 74% of patients with DLB and 66% of patients with AD had evidence of frailty.

- Anticholinergic medication burden was associated with frailty among all older adults in the study, including those without a dementia diagnosis.

1 | INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia following Alzheimer's disease (AD)[1–3] and is estimated to represent 4.2%–7.5% of dementia cases.[3] In addition to dementia, clinical features include cognitive fluctuations, rapid eye movement (REM) sleep behavior disorder, and parkinsonism, as well as neuropsychiatric symptoms (i.e., visual hallucinations, delusions, anxiety, depression, and agitation), as well as autonomic dysfunction (i.e., orthostatic hypotension, constipation, and urinary incontinence).[1,2]

Research over the past decade has revealed that the aforementioned symptoms are also prevalent in the prodromal, or early stages, of DLB,[2,4,5] which are often treated with anticholinergic medications, and may place patients at risk of polypharmacy prior to a diagnosis of dementia. Anticholinergic medications are associated with an increased risk of cognitive impairment, hospitalization, and frailty among patients with dementia.[6–9]

Notably, DLB is associated with significant cholinergic denervation,[10] which can be exacerbated by medications with anticholinergic properties prescribed to manage symptoms including urologic, psychiatric, and parkinsonian symptoms,[11,12] sleep disorders[13,14]; gait disturbances; and falls among older adults.[15] For example, up to 90% of patients with DLB may experience lower urinary tract symptoms (LUTS).[16] Among older adults, medications used for LUTS with central anticholinergic properties have been associated with an increased risk of cognitive impairment[17] and mortality relative to those medications with peripheral activity.[18]

Polypharmacy is associated with a greater risk of frailty among older adults, particularly when anticholinergic medications are used.[9,19] Frailty is defined as "a state of increased vulnerability and reduced ability to recover homeostasis after a stressful event, thereby leading to adverse health outcomes, such as falls, disability, delirium, and mortality."[20] Frailty can be measured multiple ways, including by physical features/clinical phenotype (e.g., grip strength, weight loss, activity level, and nutritional status) or deficit accumulation (e.g., number of conditions across multiple bodily systems, acute illness, injuries, and laboratory abnormalities).[21,22] Although both frailty models predict adverse outcomes including hospitalization and mortality,[23,24] it has been argued they should be used as complementary rather than interchangeable measures.[25]

To date, only one study investigated phenotypic frailty among patients with DLB and found high rates of frailty among individuals diagnosed with DLB compared to patients with AD.[26] High rates of frailty have been observed in individuals with early-stage Parkinson's disease using both phenotypic and deficit-accumulation frailty models.[27] These findings highlight the need for parallel investigation of frailty among individuals newly diagnosed with DLB.

Anticholinergic medications are associated with an increased risk of cognitive impairment and hospitalization among patients with dementia,[6–8] as well as frailty,[9] gait disturbances, and falls among older adults.[15] Similarly, there can be cumulative effects associated with taking two or more medications with anticholinergic properties, also known as anticholinergic burden.[28] Taken together, patients with DLB may be at risk for increased anticholinergic burden, and they may be more susceptible to side effects due to cholinergic denervation, which, in turn, may be associated with frailty. Little is known regarding the relationship between anticholinergic burden and frailty in patients with DLB; therefore, the objective of this study was to explore cumulative anticholinergic burden and frailty among patients with a new diagnosis of DLB relative to patients with the most common form of dementia, AD, and older adults without a diagnosis of cognitive impairment.

2 | METHODS

This cross-sectional study leveraged electronic health records and claims data between October 2015 and August 2022, from HealthPartners, an integrated health care system in the United States, that provides general medical and specialty care and insurance coverage to its subscribers.[29] The study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. The HealthPartners Institutional Review Board approved waivers of consent for use of electronic medical records for patients who have not chosen to opt out of use of their data for research. All study subjects who met study criteria were included without regard to sex, race, or ethnicity.

We utilized the Bynum-standard algorithm, validated previously in Medicare beneficiary data,[30] to identify dementia cases through claims data. DLB cases were defined as individuals with two or more claims with the International Classification of Diseases, Tenth Revision (ICD-10) code G31.83 ("*Neurocognitive disorder with Lewy bodies*"). AD cases required two or more claims with the ICD-10 code G30.X (*"Alzheimer's disease"*). The index date was defined as the first date with a documented ICD-10-coded diagnosis of DLB or AD. Patients with AD and those without an ICD-10 code of mild cognitive impairment or dementia ("controls") were matched (3:1) on age and sex to the DLB group at index. Random chart audits (5%) were conducted to confirm diagnosis.

The Anticholinergic Cognitive Burden Scale (ACB) was used to quantify anticholinergic medication burden. This scale comprises a list of medications scored as 1, 2, or 3, identified through expert consensus

to represent possible, mild, and moderate to severe anticholinergic cognitive burden, respectively. Scores are summed to determine the total ACB score. Previous studies have classified ACB into categories: no anticholinergic burden for each patient (ACB score = 0), low anticholinergic burden (ACB score = 1 or 2), moderate anticholinergic burden (ACB score = 3 or 4), high anticholinergic burden (ACB score ≥5).[31] Patient prescription claims data for the 12-month period prior to the index date were used to calculate the ACB for this study.

Frailty was assessed with the Kim's Claims-based Frailty Index (CFI), a deficit accumulation index that estimates frailty using 12 months of insurance claims data. CFI has been developed and validated using data from community-dwelling Medicare beneficiaries. The CFI score ranges between 0 and 1 and can be used as a continuous variable, with higher scores indicating greater frailty, or a dichotomous variable, with a cutoff score of ≥0.20 indicating frailty.[32] In this study, the CFI was calculated for the 12-month period prior to index. Multimorbidity was measured using the Charlson Comorbidity Index (CCI), which is the weighted sum of 19 medical conditions associated with an increased risk of mortality. Higher scores reflect more severe multimorbidity.

2.1 | Statistical analysis

Patient characteristics measured at index were compared between DLB, AD, and control groups using bivariate tests of association (analyses of variance [ANOVAs] and chi-square tests, as appropriate)[33] with accompanying post hoc comparisons using Bonferroni adjustment to account for pairwise comparisons. Pearson correlation coefficients ("*r*") between ACB and CFI scores were calculated within the total sample and by patient diagnosis, including pairwise differences to identify differences between individual groups. Logistic regression estimated the association between an ACB score ≥1 and frailty (CFI ≥0.20) within each group (DLB, AD, and controls) adjusted for patient race and the CCI. An interaction term between patient diagnosis and ACB score ≥1 was included to evaluate if a differential association existed between anticholinergic burden and frailty dependent on patient diagnosis. Secondary analysis was performed by contrasting the primary results to use of an indicator of ACB score ≥2 and continuous values of ACB. Adjusted odds ratios (aORs), 95% confidence intervals (95% CI), and *p*-values were presented and interpreted using a two-sided alpha of 0.05. Model performance was assessed using fit and discrimination statistics including area under the receiver-operating characteristic curve (AUC-ROC). All analyses were performed in R version 4.2.1.

3 | RESULTS

We identified 175 patients with DLB: the average age was 78 years (SD = 8); 42% were female. Of 2478 patients diagnosed with AD, 525 were matched to the DLB group on age and sex (3:1). In addition, 525 individuals without a diagnosis of cognitive impairment (controls) were also age- and sex-matched to the DLB group. The full sample ($N = 1225$) was predominately White (85%), non-Hispanic (81%), and ≥75 years of age (63%). A larger percentage of patients with AD self-identified as Black/African American compared to patients with DLB ($p_B = 0.015$).

RESEARCH IN CONTEXT

1. **Systematic review**: Core and supportive features of dementia with Lewy bodies (DLB) have been documented in the prodromal disease state and, therefore, individuals may be at risk for polypharmacy and anticholinergic burden before diagnosis. The emerging literature suggests that anticholinergic medications are associated with frailty among patients with dementia, but this has not been studied explicitly in DLB.
2. **Interpretation**: DLB was associated with higher rates of frailty and anticholinergic burden compared to matched controls. Patients with DLB had a greater number anti-choinergic medications compared to AD and controls. Anticholinergic medication burden was associated with frailty for all older adults in this study.
3. **Future directions**: This information may be used to develop interventions aimed at reducing anticholinergic burden among older adults with and without cognitive impairment. Additional research is needed to replicate findings in other health care systems with more diverse patient populations. Routine medication management therapy at the time of dementia diagnosis may be a useful intervention.

3.1 | Comorbidity

Patients with dementia had higher CCI (comorbidity)scores than controls. Twenty-seven percent of patients with DLB and 22% with AD had CCI scores reflecting severe comorbidity (≥5).

3.2 | Anticholinergic burden

Patients with AD or DLB dementia had higher ACB scores compared to controls; however, patients with DLB were prescribed significantly higher numbers of anticholinergic medications than patients with AD ($pB < 0.001$), with 23.4% of patients with DLB having an ACB score ≥5 compared to only 9.7% of patients with AD (Table 1).

3.3 | Frailty

Figure 1 displays the linear relationships between the patients' ACB scores plotted against their CFI values. Anticholinergic burden was positively correlated with frailty for all groups ($r = 0.30$ to 0.47), with

TABLE 1 Patient demographics and measures of frailty and anticholinergic burden at the time of index date.

	DLB (*N* = 175)	AD (*N* = 525)	Controls (*N* = 525)	*p*-value
Age at index date (years)				
Mean ± SD	78 ± 8	78 ± 8	78 ± 8	
<65	5.1%	5.0%	5.1%	
65—74	32.0%	31.8%	32.0%	
75—84	36.6%	37.0%	36.6%	
85+	26.3%	26.3%	26.3%	
Sex				
Male	58.3%	58.3%	58.1%	
Female	41.7%	41.7%	41.9%	
Race				<0.0001[2,†,‡]
White	90.3%	89.9%	78.3%	
Black/African American	2.9%	5.1%	5.0%	
Asian	2.9%	1.7%	5.5%	
American Indian/Alaska Native	0.6%	0.4%	0%	
Native Hawaiian /Pacific Islander	0.0%	0.2%	0.6%	
Multiple Races	0.6%	0.0%	0.6%	
Other	1.1%	0.4%	1.9%	
Unknown	1.7%	2.3%	8.2%	
Ethnicity				0.001[2,*,†]
Hispanic or Latino	1.1%	1.1%	0.8%	
Non-Hispanic or Latino	88.0%	84.8%	75.6%	
Unknown	10.9%	14.1%	23.6%	
Charlson Comorbidity Index				<0.0001[2,*,†]
None (0)	14.3%	19.8%	36.4%	
Mild (1–2)	38.9%	37.1%	32.4%	
Moderate (3–4)	19.4%	21.0%	17.5%	
Severe (5+)	27.4%	22.1%	13.7%	
Kim's Claims-based Frailty Index				
Mean ± SD	0.26 (0.08)	0.22 (0.08)	0.15 (0.06)	<0.001[1,*,†,‡] <0.0001[2,*,†,‡]
Not Frail (<0.2)	26.3%	42.5%	83.2%	
Frail (≥0.2)	73.7%	57.5%	16.8%	
Anticholinergic Cognitive Burden Scale				
Mean ± SD	2.57 (2.44)	1.63 (1.98)	1.10 (1.67)	<0.001[1,*,†,‡] <0.0001[2,*,†,‡]
None (0)	27.4%	38.3%	55.6%	
Low (1–2)	28.6%	36.0%	27.0%	
Moderate (3–4)	20.6%	16.0%	12.2%	
High (5+)	23.4%	9.7%	5.1%	

DLB, dementia with Lewy bodies; AD, Alzheimer's disease; ACB, Anticholinergic Cognitive Burden Scale; Controls were defined as older adults without a cognitive diagnosis who were age-/sex-matched 3:1 with clinically diagnosed DLB cases (525:175); Kim's Claims-based Frailty Index, ACB score, and CCI, Charlson Comorbidity Index; calculated using electronic medical record and prescription data in the year before index diagnosis. Pairwise comparisons considered statistically significant if Bonferroni adjusted $p < 0.05$.

[1]ANOVA.

[2]Chi-square.

*Statistical difference between DLB and control groups.

†Statistical difference between AD and control groups.

‡Statistical difference between DLB and AD groups.

N = 1225.

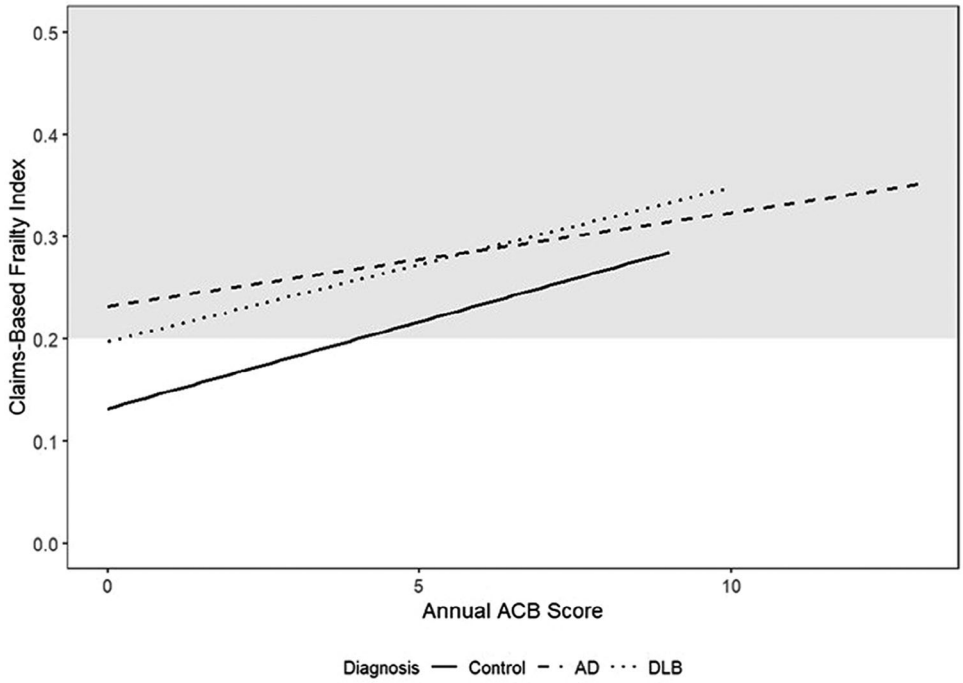

FIGURE 1 Anticholinergic Cognitive Burden scale and Kim's Claim-based Frailty Index in the year before initial dementia diagnosis. Notes: DLB, dementia with Lewy bodies; AD, Alzheimer's disease; Controls were defined as older adults without a cognitive diagnosis; AD and Controls were age-/sex-matched 3:1 with clinically diagnosed DLB cases (525:175); *r*, Pearson correlation coefficient for diagnosis group.

controls experiencing a stronger relationship between ACB and CFI ($r = 0.47$, 95% CI: 0.40–0.53) than patients with DLB (0.30, 95% CI: 0.16–0.43; $p = 0.02$) and AD (0.35, 95% CI: 0.32–0.39; $p = 0.02$). Compared to controls, diagnoses of DLB or AD were associated consistently with an increased odds of frailty, regardless of what ACB dependent variable was used (ACB score ≥1, ACB score ≥12, continuous ACB score) after matching for sex and age and controlling for race and CCI (Table 2). Specifically, when adjusting for ACB scores ≥1, patients with DLB or AD were 15.1 and 7.7 times more likely, respectively, to be classified as frail compared to control patients without dementia (aOR: 15.1, 95% CI: 7.0–33.9; aOR = 7.7, 95% CI: 4.4–13.7).

In all models, higher ACB scores were associated with a higher odds of frailty. Specifically, patients with at least one medication on the ACB list were 2.7 times (95% CI: 1.6–4.8) more likely to be frail compared to those without anticholinergic medications (Table 2). This association was not found to differ between diagnosis groups, with all interaction terms not meeting the threshold of significance ($p > 0.05$). All models demonstrated excellent discrimination when predicting frailty based on diagnosis, ACB, race, and CCI, with AUC-ROC of ≈0.86.

4 | DISCUSSION

In this study, patients diagnosed with DLB had a higher anticholinergic burden in the year prior to diagnosis compared to patients diagnosed with AD and controls. Approximately 23% of patients with DLB had high anticholinergic burden (ACB scores ≥5).[31] A recent study by García-Lluch et al.[34] revealed that the patients with dementia in their sample had higher rates of anticholinergic medications compared to controls.

Notably, Weigand et al.[35] reported that anticholinergic medication use in cognitively healthy, highly educated, and healthy older adults was associated with an increased risk of progression to mild cognitive impairment and accelerated cognitive decline among individuals with positive AD biomarkers.[35,36] Our work expands on this by including a DLB group and would suggest that irrespective of the mechanisms involved, that anticholinergic burden may differ between different forms of dementia. For example, the broad clinical phenotype associated with DLB may increase the likelihood of several providers prescribing medication for the same patient. Therefore, our current findings may have implications for the clinical care of patients who are at risk of developing dementia or patients in the early stages of neurodegenerative disease. Deprescribing interventions, in particular, should be considered at the time of dementia diagnosis.

As expected,[37] patients with dementia had significantly higher rates of frailty compared to controls, even with adjustment for anticholinergic burden and demographics. Although more than 65% of the DLB and AD groups experienced frailty, we did not observe a significant difference in frailty between DLB and AD patients. A Norwegian study also found high rates of frailty in patients with DLB and AD, with the highest rates of frailty among patients with DLB,[26] but this study did not control for anticholinergic burden, which may have contributed to an observed difference in frailty rates.

Anticholinergic medication use was associated with frailty in all older adults in this study. Although this finding is consistent with

TABLE 2 Multivariable logistic regression estimating likelihood of frailty associated with dementia subtype, anticholinergic cognitive burden, and other patient characteristics.

	Odds ratio (95% CI)		
Main effects	**ACB Score ≥1**	**ACB Score ≥2**	**ACB Continuous**
AUC-ROC (95% CI)	0.86 (0.84, 0.88)	0.86 (0.84, 0.88)	0.87 (0.84, 0.89)
Diagnosis (ref = Controls)			
DLB	**15.09 (6.95, 33.92)**	**14.34 (7.55, 27.91)**	**16.77 (8.89, 32.33)**
AD	**7.66 (4.43, 13.71)**	**9.51 (6.09, 15.27)**	**7.39 (4.74, 11.73)**
ACB Measure			
≥1, ≥2, Continuous	**2.71 (1.58, 4.81)**	**3.88 (2.30, 6.64)**	**1.41 (1.24, 1.62)**
Interaction: Diagnosis x ACB			
DLB x ACB	0.88 (0.33, 2.31)	0.85 (0.33, 2.17)	0.86 (0.68, 1.08)
AD x ACB	0.91 (0.45, 1.79)	0.64 (0.32, 1.25)	1.03 (0.85, 1.25)
Covariates			
Race (ref = White)			
Non-White	1.54 (0.99, 2.40)	**1.57 (1.01, 2.46)**	1.42 (0.91, 2.23)
Charlson Comorbidity Index (ref = 0)			
Mild (1–2)	**5.47 (3.51, 8.75)**	**5.57 (3.56, 8.93)**	**5.33 (3.41, 8.55)**
Moderate (3–4)	**9.36 (5.73, 15.70)**	**9.18 (5.59, 15.42)**	**8.71 (5.31, 14.63)**
Severe (5+)	**22.90 (13.6, 39.51)**	**21.90 (13.0, 37.93)**	**20.94 (12.41, 36.27)**

Note: Controls were defined as older adults without a cognitive diagnosis who were age-/sex-matched 3:1 with clinically diagnosed DLB cases (525:175); ACB, Anticholinergic Cognitive Burden Scale; bolded statistics indicate statistical significance ($p < 0.05$); logistic regression used to model the odds of frailty, defined as Kim's Claims-based Frailty Index ≥0.20; Kim's Claims-based Frailty Index, ACB score, and CCI calculated using electronic medical record and prescription data in the year before index diagnosis.

Abbreviations: ACB, Anticholinergic Cognitive Burden Scale; AD, Alzheimer's disease; AUC-ROC, area under the receiver-operating characteristic curve; CI, Confidence interval; DLB, dementia with Lewy bodies.

previous research,[9,38,39] it is unclear why the strongest association in our study was between patients without documented cognitive impairment relative to patients with dementia. Further research is needed. Nonetheless, cumulative anticholinergic effects may be an important predictor of frailty among individuals newly diagnosed with DLB or AD. It is possible that de-prescribing interventions at the time of dementia diagnosis may reduce the risk of frailty as the disease progresses. It is important to note that not all anticholinergic medications are necessarily inappropriate to use in older adults (e.g., medication for LUTS or depression)[40]; however, alternative pharmaceutical and non-pharmaceutical approaches should be considered where possible, and clinicians should carefully evaluate the risks and the benefits of prescribing medications for older adults.[17,40–42]

The relationship between frailty and comorbidity is not well understood.[21,43,44] Although there are similar features between these concepts, they differ in important ways.

We used a deficit-accumulation model to define frailty. This concept takes factors such as acute illness, injury, difficulty maintaining physiologic homeostasis, and abnormal laboratory values into consideration,[21] whereas comorbidity is defined as the presence of two or more medical conditions with evidence of impact on morbidity.[43] It has been suggested there is a bi-directional causal relationship between frailty and comorbidity.[44] In other words, comorbid disease may increase the risk of frailty and frailty may exacerbate comorbid conditions; however, it is possible to meet criteria for frailty without multimorbid conditions.[43] It is also possible that anticholinergic medications influence this relationship,[9,21] but further research is needed.

The strength of this study is its use of prospective naturalistic data, enabling sample sizes that would be unfeasible using other study designs and comparison of diagnostic groups. Our methods of calculating frailty, anticholinergic burden, and cholinergic burden have been validated in similar data sets. Nevertheless, this study has several limitations. One is the reliance on ICD-10 codes in electronic medical records and claims data to classify patients. However, previous research comparing dementia diagnoses from Medicare claims with clinical assessments demonstrated that administrative claims data have acceptable sensitivity and specificity,[45,46] and several studies have utilized ICD codes to identify dementia cases from these data sources.[45,47,48]

In this study, we utilized prescription claims data as a proxy for medication exposure but we are unable to determine whether patients actually took these medications, which is another limitation of research using administrative claims data. The ACB calculation did not account for short- or long-term prescriptions. In addition, we are unable to account for the use of over-the-counter medications with

anticholinergic properties. We acknowledge some of the conditions included in the CFI require the use of medications with anticholinergic properties.

Another potential limitation is that the current sample was overwhelmingly White. In particular, the group of individuals diagnosed with DLB was significantly less diverse in terms of race and ethnicity compared to patients with the control group. To date, there are very few studies on ethnically and racially diverse populations with DLB,[49,50] and there is a critical need to understand disease presentation and progression among diverse patient groups. Patients with AD and controls were matched to our population of interest: DLB. We recognize that there are differences in demographics between patients in the AD group and the control group; however, the final model was adjusted for all patient characteristics that differed between groups.

5 | CONCLUSIONS

In summary, this study is one of the first to examine the relationship between anticholinergic burden and frailty in patients newly diagnosed with DLB. Patients with DLB had higher rates of frailty and anticholinergic burden prior to a documented dementia diagnosis compared to matched controls. Although patients with DLB were prescribed significantly more anticholinergic medications than patients with AD, both groups were at an increased risk of frailty relative to controls. Anticholinergic medication use was associated with frailty for all older adults in this study, with the strongest association for patients without documented cognitive impairment. Cumulative anticholinergic effect burden may be an essential and modifiable predictor of frailty among older adults, including those newly diagnosed with dementia.

This work reinforces the importance of deprescribing medications with anticholinergic properties for older adults. This is particularly relevant for patients with DLB, who are often prescribed anticholinergic medications to manage urologic, psychiatric, sleep, and parkinsonian symptoms. Results from the current study may be used to inform prescribing practices. By reducing anticholinergic medication use and exploring alternative treatments, there is a potential to decrease the risk of frailty and improve clinical outcomes.

ACKNOWLEDGMENTS

Conceptualization: K.W., M.B., M.M., L.S., E.C., J.S., and R.R. Methodology: K.W., E.C., and R.R. Data Curation: E.C. and A.W. Formal Analysis: K.W. and E.C. Writing- Original Draft Preparation: K.W. and E.C. Writing – Review and Editing: K.W., M.B., M.M., L.S., J.K., S.C., J.K., S.P., J.S., H.N., A.W., and R.R. All authors read and approved the final version of this manuscript. This research was supported by the National Institute on Aging of the National Institutes of Health under award number R21AG074368.

CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare that are relevant to the content of this article. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The study was in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. The HealthPartners Institutional Review Board approved waivers of consent for use of electronic medical records for patients who have not chosen to opt out of use of their data for research. We excluded patients who declined permission for their medical records to be used in research.

DATA AVAILABILITY STATEMENT

Data may be accessed by contacting the primary author for a data-use agreement/provision, which requires the recipient to agree to use the data only for academic research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wyman-Chick KA, Barrett MJ, Miller MJ, et al. The relationship between anticholinergic burden and frailty in the year preceding a diagnosis of dementia with Lewy bodies. *Alzheimer's Dement*. 2024;16:e70034. https://doi.org/10.1002/dad2.70034