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Risk of decline in functional activities in dementia with Lewy bodies and Alzheimer disease

Dr. Dawn P. Gill, PhD, Dr. Thomas D. Koepsell, MD, MPH, Dr. Rebecca A. Hubbard, PhD, and Dr. Walter A. Kukull, PhD

National Alzheimer's Coordinating Center (Drs Gill, Koepsell, and Kukull) and the Departments of Epidemiology (Drs Gill, Koepsell, and Kukull), Health Services (Dr. Koepsell), and Biostatistics (Dr. Hubbard), University of Washington; Group Health Research Institute (Dr. Hubbard), Seattle, WA

Abstract

We examined risk of one-year decline in four everyday activities in patients with dementia with Lewy bodies (DLB), relative to patients with Alzheimer disease (AD). Data were from the National Alzheimer's Coordinating Center, gathered from 32 Alzheimer's Disease Centers. Participants (n = 1,880) were: 60+ years, demented with a primary clinical diagnosis of probable AD or DLB, and had a global Clinical Dementia Rating of 0.5–2. The activities were measured with the Functional Activities Questionnaire. In modified Poisson regression models adjusted for demographics, baseline activity, years from symptom onset, cognitive impairment and co-morbidities, DLB participants 67–81 years had 1.5 to 2 times increased risk of decline in performing basic kitchen tasks, engaging in games/hobbies, and paying attention/understanding, relative to AD participants of the same age ($p < 0.05$). There was no significant difference between AD and DLB participants outside of this age range. For decline in ability to go shopping alone, there was also no significant difference between AD and DLB participants. In summary, the functional course of DLB, relative to AD, may depend on the age of the patient. These findings may provide anticipatory guidance to families and health-care providers, which may be useful in the planning of care strategies.

Keywords

Dementia with Lewy bodies; Alzheimer disease; Disease progression; Prognosis; Natural history studies; Activities of daily living

INTRODUCTION

Functional decline is a highly salient end-point to examine the course of dementia. Although dementia with Lewy bodies (DLB) is the second most common neurodegenerative cause of dementia after Alzheimer disease (AD),^{1–3} few studies have examined functional decline in DLB and differences from AD. Previous studies have suggested that patients with DLB are more functionally impaired⁴ and have increased risk of mortality⁵, while others have indicated that the rate of functional decline is similar between DLB and AD.^{6, 7} In AD patients, studies have indicated that functional and cognitive decline may vary by age or gender. Specifically, studies have shown that the rate of functional decline was more rapid in those 85 years or older⁸ and cognitive functioning declined at a faster rate in males

compared to females.⁹ Whether differences in functional decline between DLB and AD vary by age or gender remains to be examined. As well, no published studies have examined decline in individual functional activities, which may have practical implications for families and caregivers.

We examined decline in four everyday activities in DLB and AD patients. We hypothesized that the cognitive domains known to be more impaired in patients with DLB, compared to those with AD, including attention, executive functioning, and visuospatial functioning,^{3, 10–13} were necessary to perform these activities. Our objectives were 1) determine if DLB patients were at increased risk of 1-year decline in their ability to perform these activities, compared to AD patients and 2) evaluate whether age or gender modified these associations.

METHODS

Data Source

We used data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS), submitted by 32 Alzheimer's Disease Centers (ADCs) located across the United States. Those data represent a clinical case series of patients assembled at individual ADCs. Most participants with dementia are referred or self-referred to ADCs for clinical evaluation. Under UDS protocol, following an initial visit, participants are to be re-evaluated annually. At each visit, data are collected using standard forms. The UDS database was implemented on September 1, 2005 and has been described in detail previously.^{14, 15}

Participants

The analytic sample was drawn from all UDS enrollees as of June 3, 2009. Eligibility criteria for the cohort were 1) clinical diagnosis of dementia, 2) age 60 years or older, 3) Global Clinical Dementia Rating (CDR) between 0.5 and 2, 4) primary clinical diagnosis of probable AD or DLB, 5) first follow-up visit made 6 to 18 months after initial visit, and 6) completed the Functional Activities Questionnaire (FAQ) at both the initial and follow-up visit. We selected age 60 as a cut-off in order to balance concerns related to losing DLB participants, whose illness may become manifest in their early 60s, and including AD participants with early-onset AD. Formation of the analytic sample is detailed in Figure 1. There were a total of 1880 participants in the analytic sample; 1761 had a primary clinical diagnosis of probable AD and 119 had a primary clinical diagnosis of DLB. All participants provided written informed consent, as approved by the Institutional Review Boards at the individual ADCs. The current study was approved by the Institutional Review Board at the University of Washington.

Outcome Measures

We examined 1-year decline in four out of ten activities measured with the FAQ. We examined ability to: 1) go shopping alone for clothes, household necessities, or groceries (shopping alone), 2) play games of skill such as bridge or chess or work on hobbies (games/hobbies), 3) perform basic kitchen tasks such as heating water, making a cup of coffee or turning off the stove (basic kitchen tasks), and 4) pay attention to and understand a TV program, book, or magazine (paying attention). These activities were selected a priori based on our hypotheses that they involved the cognitive domains of attention (paying attention), executive functioning (games/hobbies, shopping alone, basic kitchen tasks) or visuospatial functioning (games/hobbies), all shown to be more impaired in DLB compared to AD patients.^{3, 10–13} We decided to avoid activities that primarily involve memory, since previous research has suggested controversies over differences between individuals with DLB and AD in regard to memory impairment.¹³ By examining only a select number of

activities based on specific hypotheses, we sought to reduce the likelihood of finding significant differences due to chance alone.

The FAQ is an informant-based questionnaire, designed for assessment of functional status in studies of dementia, and established as reliable and valid.^{16, 17} The FAQ was administered by a trained health professional in a standardized manner at all UDS visits. For each item, the informant was asked whether the participant had any difficulty or needed help in the last four weeks. Impairment was graded on a scale from 0 (normal) to 3 (dependent); “not applicable” was a valid response if the participant never did the activity. Based on item scores at the initial and first follow-up visit, we created binary indicators of ‘decline’ for each activity (‘no decline’ was the reference category).

Primary Exposure

Our primary exposure was dementia type, a binary variable corresponding to a primary clinical diagnosis of probable AD or DLB at the initial visit. The diagnosis of probable AD was based on the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria¹⁸ and the diagnosis of DLB was based on criteria set forth in the third report of the DLB consortium.¹⁹

Confounders and Effect Modifiers

Factors considered as potential confounders were baseline activity, age, gender, race, marital status, years of education, years from symptom onset, cognitive impairment, and co-morbidities, all measured at the initial visit. Because some previous studies have found differences in patterns of functional decline by age^{8, 20} and gender⁹, we also evaluated age and gender as potential effect modifiers. Years from symptom onset was defined as the difference between age at initial visit and clinician determined age of onset of cognitive decline. We used the total score from the Mini-Mental State Examination (MMSE) as a measure of cognitive impairment, which can range from 0 to 30, with lower scores indicating greater cognitive impairment.^{16, 21} We applied the Charlson approach²² in deriving a weighted co-morbidity index, based on health conditions measured in the UDS. Four conditions (cardiac arrest, congestive heart failure, cerebrovascular disease and diabetes) were included in the index, which can range from 0 (no conditions) to 4 (all conditions).

Statistical Analysis

Modified Poisson regression modeled probability of decline as a function of dementia type. The modified Poisson regression approach estimates the risk ratio directly by using the Poisson regression model with a robust error variance estimator known as sandwich estimation.²³ This model is an alternative to logistic regression for the analysis of binary outcomes and has the advantage of directly estimating risk ratios rather than odds ratios.

For each outcome, we fit two models; all models included the primary exposure, dementia type. In Model 1, we adjusted for baseline activity (corresponding to the outcome being examined). In Model 2, we further adjusted for all remaining potential confounders. Gender, race (white vs. non-white) and marital status (married vs. not married) were entered as binary variables. Education, years from symptom onset, MMSE, and the co-morbidity index were modeled using categorical variables. In Model 2, we also investigated effect modification by gender and age separately, by testing the cross products of dementia type with gender, age and age-squared. In this model, we also accounted for clustering of participants within ADCs using Generalized Estimating Equations with an identity matrix as the working covariance structure.²⁴ This approach provides robust variance estimates via sandwich estimation, which appropriately adjusts for clustering.

In preliminary models, we categorized age in order to allow for non-linear associations between age and each outcome. We observed a U-shaped age relationship in these models. Because of the challenge of investigating effect modification using a categorical age variable, we evaluated adequacy of fit of a quadratic function for the age-outcome relationship, which approximates the observed U-shaped relationship. For each outcome, we compared p-values from models that included 1) only a linear term for age; 2) both linear and quadratic age terms; and 3) linear, quadratic and cubic age terms. We also compared the Quasilikelihood under the Independence model Criterion (QIC) statistics from the categorical, linear and quadratic age models. As a last step, we extracted the residuals from our final models and plotted these against age with a smoothing spline superimposed. Comparison of model fit criteria and residuals analysis indicated that the quadratic age model adequately fit the data and was necessary for capturing non-linear age trends. We therefore modeled age using linear and quadratic terms, with age centered at the sample mean (age 77).

Sensitivity Analyses—In order to better understand our main findings, we conducted additional analyses within the AD and DLB groups separately. For each outcome, we also re-ran our final models where: 1) all participants less than 65 years of age were excluded; 2) number of days between visits was additionally included as a possible confounder; and 3) age interaction terms were removed in order to test whether this would result in smaller main effects of DLB.

An alpha value of 0.05 was used for all statistical tests and 95% confidence intervals (CIs) are presented. Analyses were performed using SAS 9.1.3 (Cary, NC) and R 2.9.2.²⁵

RESULTS

Formation of Analytic Subsamples

The number of participants available for each outcome differed from the overall analytic sample due to additional exclusions and missing data (Table 1). For each outcome, participants were excluded if they were already dependent on the activity of interest at the initial visit or if they reportedly *never did* the activity at either visit. For all outcomes, a greater proportion of DLB participants were dependent on activities at the initial visit whereas the proportion of participants excluded due to never having done the activity was similar for the two groups. For each activity, a higher proportion of DLB participants declined in their ability to perform activities between the initial and first annual follow-up visit, compared to AD participants.

Participant Characteristics

Table 2 summarizes participant characteristics for the overall analytic sample. AD participants were on average older (77.2 vs. 73.5 years), had lower MMSE scores (21.0 vs. 22.9), and had more years since symptom onset (5.1 vs. 4.1 years), compared to DLB participants. Both AD and DLB participants were well educated (14.0 vs. 14.8 years) and most participants in both groups were white, married, had a score of zero on the co-morbidity index, and a CDR score of 0.5 or 1. The mean number of days (SD) between the initial and follow-up visit was 386.4 (55.4) for the AD group and 388.8 (53.9) for the DLB group.

Risk of 1-year Decline in Functional Activities in DLB Relative to AD

Risk ratios and 95% CIs for both models, for each outcome, are presented in Table 3. In the models that only controlled for baseline activity (Model 1), point estimates suggest that DLB participants were at increased risk of decline in all four activities, relative to AD

participants; however, differences in decline in relation to dementia type were not statistically significant. For three of the outcomes (basic kitchen tasks, games/hobbies, and paying attention), when we controlled for additional potential confounders and accounted for clustering (Model 2), the main effect of DLB was statistically significant and there was a significant interaction between age and dementia type. For the outcome shopping alone, dementia type was not statistically significant and there was no evidence of an age interaction. There was also no evidence of effect modification by gender for any of the outcomes.

Figure 2 shows results from Model 2 for the main effect of DLB on decline in games/hobbies (A), basic kitchen tasks (B), and paying attention (C), as modified by age. For each outcome, for participants 67 to 81 years of age, the DLB group was at significantly increased risk of decline compared to the AD group ($p < 0.05$). Risk of decline was lower in the DLB group than the AD group, for participants younger than 67 and older than 81; however, this difference was not statistically significant. Specifically, relative to AD participants, DLB participants between the ages of 1) 68 to 80 years, had up to 1.9 times increased risk of decline in ability to play games/work on hobbies, 2) 69 to 81 years, had up to 1.8 times increased risk of decline in ability to perform basic kitchen tasks, and 3) 67 to 81 years, had up to 1.5 times increased risk of decline in ability to pay attention/understand.

Sensitivity Analyses

In order to better understand reasons for the suggested inverse U-shaped relationships with age, we carried out analyses within AD and DLB groups separately. We examined characteristics of participants in our analyses versus those excluded due to dependence at baseline. Among AD participants, those excluded were significantly older, more cognitively impaired, and had more years from symptom onset, on average, than participants included in analyses ($p < 0.05$). A similar pattern was also seen in DLB participants. We examined proportions of AD and DLB participants who declined by age groupings. For the three outcomes where risk of decline in DLB varied by age, among AD participants, a higher proportion in the 85+ group declined compared to those 65–69, 70–74, 75–79 or 80–84. As well, for the outcome games/hobbies, a higher proportion of AD participants aged 60–64 years, declined, compared to AD participants in the other age groups. When we excluded all participants less than 65 years of age, our main findings were essentially unchanged. This was also true when we additionally adjusted for the number of days between visits. For the outcomes basic kitchen tasks, games/hobbies and paying attention, we found that removing age interaction terms led to smaller main effects of DLB. This finding suggests that if we had not examined effect modification by age, our main effects would have been attenuated.

DISCUSSION

We found a significant association between dementia type and decline in three out of four examined activities, which varied in strength and direction according to age. DLB participants 67 to 81 years of age had 1.5 to 2 times the risk of declining over 1-year in their ability to perform basic kitchen tasks, play games/hobbies and pay attention/understand, compared to AD participants of the same age. Among participants younger than 67 and older than 81, the DLB group had decreased risk of decline compared to the AD group; however, this decrease failed to reach statistical significance. For the outcome shopping alone, no age interaction was detected and the main effect of DLB was not statistically significant.

We did not expect to find the suggested inverse U-shaped association with age. Because AD and DLB participants who were excluded from our analyses (due to dependence at baseline) were similar in demographic and health-related characteristics, we concluded that selection

bias was an unlikely explanation for our findings. Furthermore, it seems unlikely that selection bias could account for our findings since it would have to vary with diagnosis group and age. Nonetheless, these observations impact the generalizability of our findings to similar DLB and AD patients who have not yet become dependent and who are in the earlier stages of their diseases. Patients with DLB who survive to age 85 may be a less vulnerable subgroup of patients with DLB; this could account for the trend toward decreased risk seen in the oldest participants with DLB, relative to AD, in our study.

A greater proportion of DLB participants were more severely impaired at baseline, compared to AD participants, suggesting that individuals with DLB may decline more rapidly after dementia onset. This lends support for our findings of increased risk of decline in DLB, relative to AD, for individuals in the 67 to 81-year age range. As well, we found similar patterns of effect modification by age across several activities, arguing against the idea that our findings are a statistical fluke. Our sensitivity analyses suggested that the trend of decreased risk of decline in the oldest participants with DLB, compared to AD, may be driving the age interactions. This agrees with previous findings in AD patients, where more rapid progression of dependency was seen in those 85 years or older.⁸ It is unclear why there was also a trend toward decreased risk in the youngest DLB participants, relative to AD participants, however, one possible explanation is that the younger AD participants included in our study may have a more aggressive form of the disease.

Cross-sectional studies have suggested that DLB patients have more severe functional impairment, worse quality of life, and use more health-care resources, compared to AD patients.^{4, 26–28} Studies have shown that DLB patients also have increased risk of mortality, shorter survival times, faster time to hospitalization or institutionalization, and faster cognitive decline.^{5, 6, 29, 30} Collectively, these findings are in line with the results found for most participants in this study (those 67 to 81 years old). Galvin et al.² reported that numerous personality traits, including relinquishing hobbies and growing apathy, distinguished DLB from AD patients. These personality traits may mediate the effect of DLB on functional decline, providing a possible explanation for our results.

In contrast, a number of studies have found no significant differences between AD and DLB in regard to cognitive decline^{5, 6, 29, 31} and in progression of functional impairment.^{6, 7} There are many possible reasons for discrepancies with our findings. As suggested by Stavitsky et al.⁷, the studies that examined progression of functional impairment,^{6, 7} may have been underpowered to detect differences between groups. As well, these studies may have controlled for factors that are specific to one disease process and, in effect, may have at least partially blocked the causal effect of dementia type. For example, extrapyramidal signs may mediate the effect of DLB on rate of functional decline⁴ and adjusting for this factor in multivariable analyses may lead to biased results. Additionally, neither study tested whether the relationship varied by age. If age interactions had not been directly tested in our models, our main effects would have been attenuated due to the averaging of effects across ages.

Limitations of our study deserve comment. Compared to a neuropathological diagnosis, it is likely that some misclassification of our dementia groups occurred. The NACC database includes neuropathology data but few participants in the UDS have died and undergone autopsy to date; accordingly, examining autopsy cases is not possible at this time. Even so, we argue that our approach is a pragmatic one since a clinical diagnosis is the only option for an individual when they are alive and thus, when treatment plans need to be made. While the FAQ has been used to assess functional status in studies of dementia, including clinical trials involving mild to moderate AD patients,^{16, 32} it was not designed for assessment of individuals with DLB. Currently, there is no instrument that has been specifically designed for use in DLB patients.

As discussed by Morris et al.,¹⁵ demented individuals from ADCs are unlikely to be representative of the general population of older adults suffering from dementia. As well, the majority of participants in our sample were white and highly educated. Consequently, caution should be taken in generalizing results from our study to populations that may differ demographically. Our findings should also be interpreted in the context of decline over a short time period (one-year). The patterns of decline in both AD and DLB patients may be different over a longer time period. Finally, we were interested in prediction of decline from the diagnosis at the initial visit. As a result, we did not examine the stability of diagnoses and it is unknown whether any participants' diagnoses changed over time.

In summary, our findings suggest that the functional course of DLB, relative to AD, may depend on the age of the patient. In our study, DLB participants between the ages of 67 and 81 had varying levels of increased risk of functional decline, relative to AD participants of the same age. These findings may influence clinical trials that aim to slow decline in AD and DLB, by providing necessary information on how functional status progresses in placebo or usual-care groups and how treatments may modify this progression. As well, our findings may provide anticipatory guidance to families and health-care providers. In the early stages of these disease processes it is critical to recognize how everyday abilities will be impacted by the disease, so that appropriate care strategies can be implemented.

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Figure 1.

Figure 2.

Table 1

Number of Participants Available for Analyses by Group and Outcome^a

	Games & Hobbies		Basic Kitchen Tasks		Paying Attention		Shopping Alone	
	AD	DLB	AD	DLB	AD	DLB	AD	DLB
Overall analytic sample	1761	119	1761	119	1761	119	1761	119
Excluded								
Dependent on activity at initial visit	310	30	266	33	168	14	501	50
Never did activity at initial visit and/or first annual follow-up visit	327	22	96	6	16	0	88	8
Missing values on covariates ^b	79	9	94	9	117	12	81	6
Data available for analysis	1045	58	1305	71	1460	93	1091	55
Decline cases	472	32	522	32	623	47	567	30

^aOutcomes are defined as 1-year decline in ability to perform activities listed in the top row.

^bParticipants were excluded if they had missing values listed for race, marital status, education, co-morbidity index, Mini-Mental State Examination score, or time since symptom onset. Data were complete for age and gender.

Abbreviations: AD, Alzheimer disease; DLB, dementia with Lewy bodies.

Table 2

Version 1. Description of Overall Analytic Sample at Initial Visit

Characteristics	AD (n = 1761)	DLB (n = 119)
	No. (%) ^a	No. (%) ^a
Age, y		
60–64	119 (6.8)	11 (9.2)
65–69	173 (9.8)	26 (21.8)
70–74	317 (18.0)	31 (26.1)
75–79	465 (26.4)	26 (21.9)
80–84	382 (21.7)	18 (15.1)
85–104	305 (17.3)	7 (5.9)
Gender		
Female	944 (53.6)	31 (26.1)
Race ^b		
White	1430 (81.4)	110 (92.4)
Marital status ^c		
Married	1169 (66.6)	105 (88.2)
Education, y ^d		
0–12	253 (14.5)	13 (10.9)
12–15	744 (42.5)	44 (37.0)
16–17	400 (22.8)	30 (25.2)
18–24	354 (20.2)	32 (26.9)
Co-morbidity score ^e		
0	1475 (84.4)	99 (86.1)
1	253 (14.5)	12 (10.4)
2–3	20 (1.1)	4 (3.5)
CDR score, %		
0.5	28.7	31.9
1	54.3	47.1
2	17.0	21.0
MMSE score ^f		
0–10	81 (4.7)	2 (1.7)
11–15	167 (9.6)	6 (5.3)
16–20	447 (25.7)	24 (21.1)
21–25	707 (40.7)	43 (37.7)
26–30	335 (19.3)	39 (34.2)
Years from symptom onset, y ^g		
0–1	133 (7.9)	16 (14.0)
2–3	485 (29.0)	35 (30.7)
4–5	446 (26.7)	31 (27.2)
6–7	320 (19.1)	21 (18.4)
8–9	128 (7.7)	9 (7.9)

Characteristics	AD (n = 1761)	DLB (n = 119)
	No. (%) ^a	No. (%) ^a
10–31	161 (9.6)	2 (1.8)

^aPercentages were calculated excluding those with missing values.

^b_{n=1757} (AD)

^c_{n=1755} (AD)

^d_{n=1751} (AD)

^e_{n=1748} (AD), _{n=115} (DLB)

^f_{n=1737} (AD), _{n=114} (DLB)

^g_{n=1673} (AD), _{n=114} (DLB)

Abbreviations: AD, Alzheimer disease; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating.

Table 2

Version 2. Description of Overall Analytic Sample at Initial Visit

Characteristic	AD (n = 1761)	DLB (n = 119)
Age, y	77.2 ± 7.7	73.5 ± 6.8
Gender, %		
Female	53.6	26.1
Race ^a , %		
White	81.4	92.4
Marital status ^b , %		
Married	66.6	88.2
Education ^c , y	14.0 ± 3.7	14.8 ± 3.5
Co-morbidity score ^d , %		
0	84.4	86.1
1	14.5	10.4
2–3	1.1	3.5
CDR score, %		
0.5	28.7	31.9
1	54.3	47.1
2	17.0	21.0
MMSE score ^e	21.0 ± 5.2	22.9 ± 4.9
Years from symptom onset ^f , y	5.1 ± 3.4	4.1 ± 2.4

Values are presented as mean ± standard deviation unless otherwise indicated. Percentages were calculated excluding those with missing values.

^a n=1757 (AD)

^b n=1755 (AD)

^c n=1751 (AD)

^d n=1748 (AD), n=115 (DLB)

^e n=1737 (AD), n=114 (DLB)

^f n=1673 (AD), n=114 (DLB)

Abbreviations: AD, Alzheimer disease; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating.

Table 3

Results from Modified Poisson Regression Analyses^a

Statistical models	Basic Kitchen Tasks (n = 1376)			Games & Hobbies (n = 1103)			Paying Attention (n = 1553)			Shopping Alone (n = 1146)		
	RR (95% CI)	P		RR (95% CI)	P		RR (95% CI)	P		RR (95% CI)	P	
Model 1 ^b												
Dementia type (Main effect of DLB) ^c	1.13 (0.86–1.47)	.38		1.25 (0.99–1.59)	.06		1.13 (0.92–1.40)	.25		1.03 (0.81–1.32)	.79	
Model 2 ^d												
Dementia type (Main effect of DLB)	1.73 (1.32–2.28) ^e	<.001		1.71 (1.32–2.22) ^e	<.001		1.44 (1.17–1.76) ^e	<.001		1.12 (0.89–1.40)	.35	
Dementia type × age (10 years)	0.70 (0.44–1.11)	.13		0.63 (0.40–0.99)	.05		0.78 (0.59–1.05)	.10		---	---	
Dementia type × age ² (10 years)	0.45 (0.22–0.92)	.03		0.48 (0.27–0.85)	.01		0.67 (0.47–0.96)	.03		---	---	

^aOutcomes are defined as 1-year decline in ability to perform activities listed in the top row.

^bAdjusted for baseline activity.

^cProbable Alzheimer disease is the reference category.

^dAdjusted for baseline activity, age, age², gender, race, marital status, education, years from symptom onset, co-morbidity index, Mini-Mental State Examination score and accounted for clustering via Generalized Estimating Equations. For all outcomes except *shopping alone*, models also include dementia type × age and dementia type × age² interaction terms. Age was centered in all models.

^eDue to age interactions, RRs (95% CIs) correspond to the risk of decline for a 77-year old (mean age in sample).

Abbreviations: RR, risk ratio; CI, confidence interval; P, P Value; DLB, dementia with Lewy bodies.