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Differences in rate of functional decline across three dementia types

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Abstract

Background—To estimate differences in rates of functional decline in Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and vascular dementia (VaD) and whether differences vary by age or sex.

Methods—Data came from 32 U.S. Alzheimer's Disease Centers. The cohort of participants (n = 5,848) were 60+ years and had clinical dementia with a primary etiologic diagnosis of probable AD, DLB or probable VaD, a Clinical Dementia Rating-Sum of Boxes score < 16, and duration of symptoms ≥ 10 years. Dementia diagnoses were assigned using standard criteria. Annual mean rate of change of the Functional Activities Questionnaire (FAQ) score was modeled using multiple linear regression with Generalized Estimating Equations, adjusted for demographics, co-morbidities, years since onset and cognitive status (mean follow-up = 2.0 years).

Results—FAQ declined more slowly over time in those with VaD compared to AD (difference in mean annual rate of change: -0.91; 95% CI: -1.68, -0.14). VaD participants also declined at a slower rate than DLB participants but this difference was not statistically significant (-0.61; 95%

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CI: -1.45, 0.24). There was no significant difference between DLB and AD. Within each group, rate of decline was more rapid for the youngest participants.

Conclusions—In this sample, findings suggested that VaD patients declined in their functional abilities at a slower rate compared to AD patients and that there were no significant differences in rate of functional decline between patients with DLB compared to those with either AD or VaD. These results may provide guidance to clinicians about average expected rates of functional decline in three common dementia types.

Keywords

Alzheimer's disease; dementia with Lewy bodies; vascular dementia; disease progression; instrumental activities of daily living; functional decline

1. Introduction

Progression of impaired functioning can lead to decreased quality of life for patients with dementia and increased burden on families, caregivers and the health-care system [1-3]. Patterns of impairment in instrumental activities of daily living (IADLs) may vary across types of dementia. Although vascular dementia (VaD) and dementia with Lewy bodies (DLB) are among the most common forms of dementia in older adults [4, 5], after Alzheimer's disease (AD), little research has examined functional decline in these dementia types and whether differences exist among them.

Of existing studies, low power or methodological limitations, such as cross-sectional designs or adjustment for intermediate variables specific to a particular diagnosis, may have contributed to conflicting conclusions [6-10]. In addition, no published studies have examined whether any differences in the rate of functional decline among dementia types may vary by either age or sex, despite evidence suggesting that these may be important factors to examine [11-14]. Additional research in large, well-characterized populations with longitudinal follow-up is needed to better understand functional decline trajectories in these common dementia types.

This study had three aims: 1) to estimate the rate of functional decline in persons with AD, DLB and VaD; 2) to determine the extent to which the rate of functional decline differs among these dementia types; and 3) to evaluate whether any differences in the rate of functional decline among these dementia types vary by age or sex. The goal of this research was to provide anticipatory guidance to families, caregivers and health-care providers, which may be useful in the planning of care strategies.

2. Methods

2.1. Setting

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. The UDS began in September 2005 and represents a clinical case series of well-characterized patients assembled at the individual ADCs [15, 16]. Under UDS protocol, following an initial visit, patients are to be re-evaluated annually. At each visit, data were collected using standard forms. The Institutional Review Board at the University of Washington approved this study. Informed consent was obtained from all participants and informants at the individual ADCs. Data obtained from NACC were de-identified.

2.2 Study participants

We studied all participants as of June 1, 2011 who had clinical dementia and a primary etiologic diagnosis of probable AD, DLB or probable VaD, at any UDS visit. The first visit at which a participant was given a qualifying diagnosis was defined as the index visit. Visits prior to the index visit were excluded. We further restricted our sample to those who were 60 years of age or older at the index visit. Next, we restricted the sample to those that had a Clinical Dementia Rating-Sum of Boxes (CDR-SB) score less than 16, to exclude participants with severe dementia at the initial visit [17]. Lastly, we restricted the sample to those whose clinician-determined age of onset of cognitive decline was known to be 10 years or less before the index visit, and who had a Functional Activities Questionnaire (FAQ) completed for at least one visit (i.e., at least half of the individual items on the FAQ had to be completed without a not-applicable response). Participants made between one and six visits, depending on date of enrollment and retention.

2.3. Data

Participants were evaluated using a standard protocol [16]. The outcome measure was the total score on the FAQ at each visit. The FAQ was designed for assessment of functional status in studies of dementia, and has been established as reliable and valid [18, 19]. It is administered to an informant by a trained health professional and consists of 10 items that measure the patient's ability to perform IADLs in the past four weeks (i.e., pay bills/balance checkbook, assemble tax records/business affairs, shop independently, take part in games/hobbies, perform basic kitchen tasks, prepare a balanced meal, comprehend current events, pay attention to/understand a TV program or reading material, remember important things such as appointments, travel out of the neighborhood). Each item is rated on a four-point scale (0 = normal; 1 = has difficulty, but does by self; 2 = requires assistance; 3 = dependent). A total score is calculated by summing the items (range 0 to 30), where higher scores indicate greater impairment [19].

Training and written guidelines that accompany UDS forms promote uniform assignment of clinical etiologic diagnoses of dementia across ADCs. Published diagnostic criteria were adopted as part of the UDS including, the NINCDS-ADRDA criteria for the diagnosis of probable AD [20], criteria set forth in the third report of the DLB consortium for the diagnosis of DLB [21], and the NINDS-AIREN criteria for the diagnosis of probable VaD [22]. To decrease the likelihood of exposure misclassification, we excluded participants with a primary diagnosis of possible AD and possible VaD from the AD and VaD groups, respectively. In the current version of the UDS, a diagnosis of DLB refers to either possible or probable DLB. Following UDS protocol, only one condition (i.e., probable AD, DLB or probable VaD) can be marked as primary. While groups were formed on the basis of the primary clinical diagnosis, participants may have had other etiologic dementia diagnoses that were believed to be contributing to cognitive impairment. Depending on the ADC, clinical etiologic dementia diagnoses are assigned by either a single clinician or through a consensus process after the visit.

We considered age, sex, race, marital status, years of education, years since symptoms began, co-morbidities, and degree of cognitive impairment as potential confounders, using values from the index visit. We applied a tailored version of the Charlson approach [23] in deriving a weighted co-morbidity index, based on health conditions measured in the UDS (cardiac arrest, congestive heart failure, diabetes). The total score on the Mini-Mental State Examination (MMSE) was used to measure cognitive impairment. We also evaluated age and sex as effect modifiers, in part because many activities may be considered sex-specific, particularly among the current generation of older adults.

2.4. Analysis

We fit multiple linear regression models using Generalized Estimating Equations (GEE) with an independence working correlation structure [24]. The GEE approach provides robust variance estimates and appropriately accounts for clustering at the participant- and ADC-level.

Functional decline was defined as the annual mean rate of change of the FAQ score following the index visit. Diagnostic group (modeled as two indicator variables), time in years since the index visit (modeled as a continuous linear variable) and the interactions of group by time were included as model predictors. In the adjusted model, sex, race, marital status, co-morbidity index, education (less than high school, high school degree, bachelor's degree, graduate degree), years since symptom onset (0-1, 2-3, 4-5, 6, 7-8, 9-10) and MMSE (0-5, 6-10, 11-15, 16-20, 21-25, 26-30), were also included and modeled categorically (see Table 1 for categories not detailed). Age was modeled as a continuous linear variable, centered at the sample mean (77 years). We also examined interactions of age and sex with the group and time variables.

In the UDS, missing values for items on the FAQ are not permitted, however, “not-applicable (i.e., never did)” is an allowable response if the participant never did the activity. Even one not-applicable response precludes calculation of a FAQ score. This approach is unique to the UDS and varies from that suggested by Pfeffer et al. [19] where for items that were never done, participants are assigned a score of 0 if they “never did, but could do now” or a score of 1 if they “never did and would have difficulty now”. We chose to replace not-applicable responses with the mean of completed FAQ items on each participant-visit, if at least half of the items were completed (i.e., the FAQ was administered and less than five of the items had not-applicable responses). We used this approach because we felt it was similar in nature to the original methodology used by the authors of the FAQ [19].

Multiple imputation [25] was used for confounding variables with missing values. We used Multiple Imputation by Chained Equations (MICE) [26] to replace each missing value with a set of 20 imputed values and included all variables from our adjusted GEE model in our imputation model. Imputations were generated using logistic regression (co-morbidity index), polytomous unordered regression (race, marital status), and predictive mean matching (education, MMSE). We fit our adjusted GEE model using each of the 20 data sets, in parallel, and combined the results using standard formulas described by Rubin [25].

We re-ran the analyses after excluding participants who had at least one co-morbid condition at their index visit that could have affected progression of their dementia (vitamin B12 deficiency, thyroid disease, alcohol abuse, other substance abuse, other major psychiatric illness, hydrocephalus, traumatic brain injury, central nervous system neoplasm). We also re-ran the analyses and additionally adjusted for interaction terms of time by each covariate in order to account for possible confounding of the differences in rates of change between groups. Within the AD group, we sought to understand whether there were differences between patients who also had DLB or vascular conditions (possible VaD, probable VaD, stroke) considered to be contributing to cognitive impairment and patients who did not. To do this, we compared rates of decline among three sub-groups from the AD group: i) AD with no DLB or vascular (AD+No DLB or Vasc); ii) AD with DLB but not vascular (AD+DLB); iii) AD with vascular but not DLB (AD+Vasc). All statistical analyses were performed using R version 2.13.1 [27]. An alpha value of 0.05 was used for all statistical tests and 95% CIs are presented.

3. Results

Participant inclusion for the final analytic sample is detailed in Figure 1. There were 8,003 participants who had clinical dementia and a primary diagnosis of probable AD, DLB or probable VaD, at any UDS visit. Applying our inclusion criteria yielded an analytic sample of 5,848 participants: 5,295 with AD, 415 with DLB and 138 with VaD. Participants with only one visit ($n = 2,690$) contributed solely to estimation of the mean FAQ at that visit. Participants with two or more visits ($n = 3,158$) contributed to the longitudinal analysis (longitudinal subset). Overall, these participants had a mean follow-up from their index visit of 2.0 years, with a maximum follow-up of 5.4 years. The mean follow-up time was similar among the three groups (see Table 1). The number of visits made, by diagnosis group, is also shown in Table 1 for the overall analytic sample and the longitudinal subset.

By using a straightforward approach of replacing not-applicable responses on individual FAQ items with the mean of completed FAQ items (on each participant-visit), we minimized the total number of subjects and visits that would be lost for our analysis (see Figure 1). The amount of visit-level data that was imputed was minimal for six items ($<5\%$ within each diagnostic group). For the other four items (pay bills/balance checkbook, assemble tax records/business affairs, take part in games/hobbies, prepare a balanced meal), we imputed between 10-19% of the visit-level values. For most items, proportions of imputed values were similar across the different diagnostic groups. For the item ‘take part in games/hobbies’, there was a higher proportion of values imputed in the VaD group (18%) compared to either the AD or DLB groups (12% in each). As well, for the item “prepare a balanced meal”, about 19% of the visit-level values were imputed in the DLB group compared to 15% in the AD group and 12% in the VaD group.

Participant characteristics at the index visit are shown in Table 1. Characteristics are presented for the total analytic sample and separately for the longitudinal subset. Within the total analytic sample, the DLB group was on average younger and had a lower proportion of females. The VaD group had a higher proportion of African-Americans. Marital status also varied by group, with about one-half of the VaD group, close to two-thirds of the AD group, and over 80% of the DLB group, being married or living as married. Approximately 15% of AD and DLB participants and 30% of VaD participants had a score of one or more on the co-morbidity index. All groups were highly educated and mean values for years since symptom onset, MMSE, CDRSB, and FAQ were similar across groups. The longitudinal subset was very similar to the overall analytic sample with a few exceptions. Specifically, within the VaD group, participants within the longitudinal subset were slightly younger on average, a smaller proportion were female, a higher proportion were married, and participants were slightly less advanced at the index visit according to MMSE, CDR-SB, and FAQ scores. Five covariates that were included in our multivariable models had missing values that were subsequently imputed using MICE. The proportion of missing values was similar across the diagnostic groups for all variables (see Table 1 footnotes).

In our analytic sample, 76% of participants received their diagnosis via a consensus process, while the other 24% were assigned a diagnosis by a single clinician. While diagnostic groups were formed on the basis of the primary clinical etiologic diagnosis, participants could have had other etiologic dementia diagnoses that were considered to be contributing to their cognitive impairment. Within the AD group, 2% of participants also had DLB marked as a contributing condition and 4% had a vascular condition (possible VaD, probable VaD, or stroke). Within the DLB group, 19% had either probable or possible AD listed as a contributing condition and 5% had a contributing vascular condition. In the VaD group, 39% had either possible or probable AD and 3% had DLB listed as conditions that were contributing to their cognitive impairment.

Table 2 shows mean FAQ scores by time in study, rounded to the nearest year. As expected, as time in study increased, so did the mean FAQ score (i.e., functioning declined). The mean FAQ score was 16.3 at the index visit (time zero) and increased to 25.1 at year 5. Due to both time of enrollment and retention, the number of observations available decreased with time.

The main results are presented in Table 3. Results from the unadjusted model (Model A) and the adjusted model (Model B) were similar in direction and statistical significance. In the adjusted model, none of the interaction terms with sex were significant. In other words, differences in rate of functional decline among groups did not vary by sex and rate of decline within each group also did not vary by sex. We also found no evidence that differences in rate of change of FAQ between groups varied significantly by age. These interaction terms were therefore excluded from our final models (i.e., three-way interactions terms of age $\times$ group $\times$ time). We did, however, find that the rate of change within each group decreased linearly as age at the index visit increased (age $\times$ time coefficient: $p = 0.005$). Accordingly, all two-way interaction terms with age (i.e., age $\times$ group and age $\times$ time) were included in our final models. Due to the inclusion of these interaction terms, baseline differences in mean FAQ and the mean rate of change of FAQ by group should be interpreted for a 77-year old, whereas differences in mean rate of change of FAQ between groups can be interpreted for any age.

From the adjusted model (Model B), at the index visit, DLB participants who were 77-years old had FAQ scores that were 3.29 points higher (i.e., worse) (95% CI: 2.45, 4.13) than AD participants, whereas FAQ scores were not significantly different between VaD and AD participants (mean difference: 1.03; 95% CI: -0.30, 2.35). In addition, at the index visit, VaD participants who were 77-years old had FAQ scores that were 2.27 points lower (95% CI: -3.87, -0.66) than DLB participants.

All groups had a positive mean rate of change in the FAQ, meaning that they were declining in their functional abilities over time. Specifically, for a 77-year old, the FAQ score increased on average by 2.52 points per year (95% CI: 2.34, 2.71) in the AD group, 2.22 points per year (95% CI: 1.74, 2.69) in the DLB group and 1.61 points per year (95% CI: 0.85, 2.37) in the VaD group. Participants with VaD deteriorated more slowly over time than AD participants (difference in mean annual rate of change: -0.91; 95% CI: -1.68, -0.14). When VaD and DLB were compared, there was no significant difference in mean annual rate of change of FAQ (-0.61; 95% CI: -1.45, 0.24). There was also no significant difference between DLB and AD in mean annual rate of change of FAQ (-0.31; 95% CI: -0.81, 0.19).

Figure 2 shows the rate of change within each group as a function of age at index visit (from Model B). While all groups were declining in functional abilities over time, this decline was steepest for the youngest participants in each group. For example, in a sample of persons age 65 with DLB, the mean FAQ score increased by about 2.5 points per year (95% CI: 1.9, 2.9) whereas in a sample of persons age 90 with DLB, the mean FAQ score increased by about 2.0 points per year (95% CI: 1.5, 2.5).

We found similar results in Model C after excluding those with at least one co-morbid condition that could have affected progression of dementia. Differences notable in Model C included the mean rate of change in the VaD group being about one-half point smaller, leading to a larger difference in the annual rate of change between the VaD and DLB groups, which became marginally significant in this reduced subset (-1.15; 95% CI: -2.36, 0.05). When we re-ran Model B and additionally adjusted for interaction terms of time by

each covariate, the results for differences in rate of decline between groups were very similar (data not shown).

We also ran a sensitivity analysis to compare rates of decline among sub-groups within the AD group. When we compared sub-groups taken from our probable AD group (“AD+DLB” vs. “AD+No DLB or Vasc”), there was no significant difference in mean annual rate of change of FAQ (0.06; 95% CI: -0.57, 0.69). As well, there was no significant difference in mean annual rate of change of FAQ between “AD+Vasc” and “AD+No DLB or Vasc” (0.01; 95% CI: -0.76, 0.79).

4. Discussion

In a sample of patients from 32 ADCs in the US, patients with a primary clinical diagnosis of VaD declined in their functional abilities at a slower rate, compared to those with an AD diagnosis, after adjustment for age, sex, race, marital status, education, co-morbidities, years since symptom onset and cognitive status. The difference in rate of decline between the VaD and AD groups did not vary significantly by age at the index visit or sex. VaD participants also declined at a slower rate than DLB participants but this difference was not statistically significant. When participants with co-morbid conditions that may have affected progression of dementia were excluded, this finding was marginally significant, suggesting that VaD patients without such co-morbidity may also decline more slowly than DLB patients. Rate of functional decline was not significantly different between DLB and AD. Within each group, rate of decline was more rapid for the youngest participants.

Our findings at baseline agree with cross-sectional studies that have suggested that DLB patients, compared to AD patients, have more severe functional impairment [8, 9]. Our findings are also similar to previous studies that indicated the rate of functional decline was not significantly different between AD and DLB [7, 10]. This is despite the fact that these former studies had limited power to detect differences and may have over-controlled for factors that could block the effect of the specific etiologic diagnosis on rate of decline (e.g., extrapyramidal signs, which are clinical consequences of DLB). Our findings that VaD and AD patients were similar in regard to their limitations on instrumental activities of daily living at baseline are in agreement with a recent cross-sectional study [6]. In addition, even though our sample of VaD patients were mostly Caucasian, our findings are in agreement with a previous study conducted in an African-American population, which found that those with VaD declined at a slower rate than those with AD [28].

Despite these similarities, some longitudinal studies that have examined endpoints closely related to functional abilities have shown that DLB patients have shorter survival times and faster time to institutionalization, compared to AD patients [7, 29]. As well, our finding suggesting that rate of functional decline within each dementia type was steeper for the youngest patients, does not agree with a study conducted in AD patients, which reported that rate of functional decline was more rapid in those 85 years or older [13]. This discrepancy may be due to the fact that the cited study examined basic activities of daily living whereas our study focused on IADLs.

Similar to Stavitsky et al. [10], our findings suggest that differences between patients with DLB and AD appear most pronounced early in the disease course. As these patients progress to more advanced stages of dementia, they appear to be similar in their impairment in IADLs. McKeith and colleagues [8] concluded that more severe functional impairment seen in DLB patients, compared to AD patients with similar cognitive scores, was related to extrapyramidal motor dysfunction. In our sample, the combined effects of cognitive and non-cognitive manifestations may have led to the finding of DLB patients being more

functionally impaired at baseline. When we examined the gait item from the Unified Parkinson's Disease Rating Scale Part III motor examination, we found that 76% AD patients and only 20% of DLB patients had a "normal" gait at baseline. After 5 years, only 60% of AD patients had a gait that was considered to be normal. These findings support the possibility that the emergence of motor signs in AD patients, which have been previously shown to predict functional decline [30], may have contributed to the finding of no significant difference in rate of functional decline between AD and DLB.

Our findings involving the VaD group are similar to Nyenhuis et al. [28] and suggest that VaD is a progressive disorder but may not progress as rapidly as AD or DLB. In our sample, we detected no significant differences in functional impairment between patients with VaD and AD at baseline, but over time, we found that VaD patients declined at a slower rate than AD patients. This is consistent with slower rate of decline in the placebo arms of randomized controlled trials with subjects with VaD compared to subjects with AD (combined with cerebrovascular disease) [31]. It is possible that patients with VaD in our study experienced vascular insults (e.g., stroke) near study enrollment, closer in time to when the diagnosis of VaD was made. Over the follow-up period, these patients may have been recovering from these vascular insults and thus, were slowly improving over time, providing one possible explanation for the finding of slower decline in VaD. Alternatively, patients within the VaD group may represent patients with a milder form of the disease if those with severe vascular disease did not enroll or did not remain under follow-up because of severe disability or death.

We defined our diagnostic groups based on the primary clinical etiologic diagnosis of dementia, with or without other contributory etiologic dementia diagnoses, in order to reflect how these dementias present and are classified in clinical practice. The majority of participants in our study received their diagnosis via a consensus process, thus strengthening the certainty of the primary clinical etiologic diagnosis. Additionally, for the AD and VaD groups, we only considered those with primary clinical diagnoses of probable AD and probable VaD, respectively. When we examined sub-groups within our largest diagnostic grouping (AD group), we found that there were no significant differences in rates of decline between patients with a primary clinical diagnosis of probable AD without DLB or vascular conditions and patients with a primary clinical diagnosis of probable AD who also had DLB or a vascular condition (i.e., possible VaD, probable VaD, stroke). These findings suggest that within our sample, the addition of other dementia processes do not influence rates of functional decline.

It is unclear why the rate of decline was greater in those who were younger at the start of our study (e.g., 60 to 65 years), but perhaps these individuals had more aggressive forms of the disease, compared to those who were still living with these dementias at age 90 or older. Alternatively, this finding could represent a ceiling effect in the older participants in our study, since these individuals had higher FAQ scores at baseline and therefore less opportunity for decline over time. For example, participants aged 60 to 69 years at the start of our study had significantly lower mean FAQ scores than participants between the ages of 80 and 89 or 90 and above [mean (SD) for 60-69 years: 15.2 (8.1) vs. 17.2 (8.4) for 80-89 years and 19.6 (8.1) for 90 and above; $p < 0.05$].

Due to their recency in the literature, the UDS has yet to implement the new AD clinical criteria [32] and as a result, the former AD criteria [20] were used in this study. Although this may be viewed as a strength of our study (i.e., the same clinical criteria were used for all participant-visits), we cannot rule out possible variation across centers in how clinical criteria were applied. This may have led to misclassification in the primary clinical etiologic diagnoses of dementia. While we consider this to be a possibility, the UDS is administered

as a standard instrument, separate from protocols already in use at the individual ADCs and measures have been taken to promote standardization, including training meetings and detailed documentation (i.e., Coding Guidebook) accompanying the UDS Data Forms [16].

Other limitations of our study warrant consideration when interpreting our results. While our total study sample size was large, the average time that participants were followed was relatively short. Of the participants contributing to the longitudinal model, 45% completed a total of 2 visits (i.e., had been followed for approximately one-year). This should be taken into consideration when interpreting our results. As well, for any of our comparisons involving the VaD group, mean differences were estimated with less precision (i.e., larger 95% CIs) due to the smaller group size.

The FAQ was specifically developed for studies of dementia and measures functional impairment due to cognitive loss [18, 19]. Since there are many reasons for functional impairment in older adults, using a measure such as the FAQ will increase the likelihood that the measured functional impairment is due to dementia. A limitation of using the FAQ in our study is that it has been most commonly used to assess functional status in mild to moderate AD patients [18, 33] and was not specifically designed for assessment of individuals with DLB or VaD.

Since the NACC database is best described as a clinical case series of patients from the individual ADCs, our analytic sample should not be considered to be a probability sample taken from the general population of older adults diagnosed with dementia. In general, ADC patients are highly educated, mostly Caucasian, and often are volunteers who may be in better health (e.g., have fewer co-morbidities) than typical patients with dementia living in the community [16]. As a result, rates of functional decline may have been underestimated in our study. Additionally, the proportion of patients with probable AD was much larger than the proportion of patients with diagnoses of DLB or probable VaD. Patients within these groups may be less representative than patients diagnosed with these diseases in the general population.

Caution should be taken when forming inferences from our study concerning the prevalence or relative frequency of patient characteristics to populations that may differ clinically and demographically. Specifically, findings may be best generalized to other similar types of patient populations, such as those arising from specialty memory clinics. Nonetheless, because the number of participants is relatively large and participants have been carefully diagnosed following a standard protocol at NIH-funded ADCs, one might reasonably expect to see similar patterns of decline within each disease category in other studies. Evidence for that similarity, however, must be provided by replication and further research.

We focused on the three most common late-life dementias due to the large predicted increase in these dementia types in the coming years [34, 35]. Understanding the functional course of AD, DLB and VaD, how it may vary by age within each of these dementia types, and how trajectories among these dementias may differ, can be important for clinical care and research. We hope that the results of this study will inform clinicians, especially those working in similar specialty memory clinics, about average rates of change in these common dementia types.

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based. The authors also thank the NIA, which provided support for the ADCs and NACC, as well as the CIHR, which provided funding for this project.

List of Abbreviations

AD	Alzheimer's disease
ADCs	Alzheimer's Disease Centers
CDR-SB	Clinical Dementia Rating-Sum of Boxes
DLB	Dementia with Lewy bodies
FAQ	Functional Activities Questionnaire
GEE	Generalized Estimating Equations
IADLs	instrumental activities of daily living
MMSE	Mini-Mental State Examination
NACC	National Alzheimer's Coordinating Center
UDS	Uniform Data Set
VaD	Vascular dementia

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Research in Context

Systematic Review: We searched PubMed (up to Dec 1, 2011) by restricting to English and combining the following search terms: (1) dementia, disease progression, activities of daily living; (2) Lewy body disease, functional abilities OR functional decline; (3) dementia, vascular, functional abilities OR functional decline. We reviewed all abstracts and then retrieved full-text articles that were deemed relevant to our study aims.

Interpretation: To our knowledge, no published studies have examined whether differences in rate of functional decline among Alzheimer's disease, dementia with Lewy bodies, and vascular dementia, vary by either age or sex. Furthermore, our study improved upon methodological limitations of former studies (e.g., cross-sectional designs, adjustment for intermediate variables, small samples).

Future Directions: Future research should attempt to replicate our findings using a population-based sample with a longer duration of follow-up. Research should also examine whether findings would be similar for populations that differ demographically.

Figure 1. Formation of Analytic Sample

Abbreviations: UDS = Uniform Data Set; AD = Alzheimer's disease; DLB = dementia with Lewy bodies; VaD = vascular dementia

* Participants were from the National Alzheimer's Coordinating Center UDS (June 1, 2011). Inclusion criteria following initial selection (Box 1) were based on values recorded for the index visit, defined as the first visit where diagnostic criteria was met

† A not-applicable response was not considered to be a completed response.

Figure 2. Mean FAQ annual change by diagnostic group and age at index visit

Circles represent point estimates and bars represent 95% confidence bands for annual mean change in the FAQ score predicted by the multiple linear regression model fit by Generalized Estimating Equations (Model B from Table 3). The model adjusted for age, sex, race, marital status, education, co-morbidity score, years since symptom onset, Mini-Mental State Examination score, age $\times$ group, age $\times$ time, and used multiple imputation for all covariates with missing data ($n = 5,848$ participants and 12,002 visits). We have estimated the trend for all ages but have presented bar plots at specific ages in order for 95% confidence bands to be shown.

Table 1

Participant characteristics at index visit

Characteristics	Total Sample (1 visit)			Longitudinal Subset (2 visits)		
	AD (N = 5295)	DLB (N = 415)	VaD (N = 138)	AD (N = 2881)	DLB (N = 222)	VaD (N = 55)
Age, y, mean $\pm$ SD	77.6 $\pm$ 7.9	74.7 $\pm$ 7.2	79.9 $\pm$ 8.1	77.2 $\pm$ 7.9	73.3 $\pm$ 7	77.8 $\pm$ 8.2
Female sex, %	57.4	25.5	52.2	54.6	21.2	40.0
Race ^{*,†} , %						
White	81.0	88.4	63.7	83.0	91.0	65.5
Black or African-American	13.4	6.8	28.3	11.6	5.4	29.1
Other	5.6	4.8	8.0	5.4	3.6	5.5
Marital status ^{*,†} , %						
Married/Living as	63.6	81.4	47.1	66.9	87.8	56.4
Widowed	25.7	12.5	39.9	23.3	6.8	29.1
Divorced/Separated	7.9	5.1	7.2	7.0	4.5	9.1
Never married/Other	2.8	1.0	5.8	2.7	0.9	5.5
Education [†] , y, mean $\pm$ SD	14.1 $\pm$ 3.8	14.5 $\pm$ 3.6	12.4 $\pm$ 4.1	14.3 $\pm$ 3.7	14.8 $\pm$ 3.3	13.1 $\pm$ 4.2
Comorbidity score ^{*,†} , %						
0	85.4	86.6	69.9	86.6	83.9	68.5
1+	14.6	13.4	30.1	13.4	16.1	31.5
Years since symptom onset, mean $\pm$ SD	4.7 $\pm$ 2.3	4.5 $\pm$ 2.2	4.3 $\pm$ 2.5	4.8 $\pm$ 2.3	4.5 $\pm$ 2.2	4.7 $\pm$ 2.7
MMSE [†] , mean $\pm$ SD	20.7 $\pm$ 5.5	21.7 $\pm$ 5.3	20.2 $\pm$ 6.2	21.3 $\pm$ 5	22.2 $\pm$ 5.5	21.8 $\pm$ 5.7
CDR-SB, mean $\pm$ SD	5.9 $\pm$ 3.2	6.1 $\pm$ 3.4	6.1 $\pm$ 3.4	5.6 $\pm$ 3	5.6 $\pm$ 3.3	5 $\pm$ 3.3
Total FAQ [†] , mean $\pm$ SD	16.1 $\pm$ 8.4	18.2 $\pm$ 8.1	17.9 $\pm$ 9	15.6 $\pm$ 8.2	17.3 $\pm$ 8.1	15.5 $\pm$ 9.6
Total number of visits made, %						
1	45.6	46.5	60.1	---	---	---
2	24.1	27.0	21.7	44.3	50.5	54.5
3	15.1	16.4	8.7	27.7	30.6	21.8
4	9.2	6.7	7.2	16.8	12.6	18.2
5	5.2	3.4	2.2	9.5	6.3	5.5

Characteristics	Total Sample (1 visit)			Longitudinal Subset (2 visits)		
	AD (N = 5295)	DLB (N = 415)	VaD (N = 138)	AD (N = 2881)	DLB (N = 222)	VaD (N = 55)
6	0.9	0.0	0.0	1.7	0.0	0.0
Length of follow-up, mean ± SD	---	---	---	2.0 ± 1.1	1.8 ± 0.9	1.8 ± 1.0

Abbreviations: AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; VaD = Vascular dementia; MMSE = Mini-Mental State Examination; CDR-SB = Clinical Dementia Rating - Sum of Boxes; FAQ = Functional Activities Questionnaire

Total sample: race (14, 2, 0); marital status (30, 1, 2); co-morbidity score (40, 6, 5); MMSE (115, 12, 5); total FAQ (39, 4, 1)

Longitudinal subset: race (7, 0, 0); marital status (9, 1, 0); education (16, 0, 1); co-morbidity score (23, 4, 1); MMSE (48, 6, 0); total FAQ (25, 3, 1)

* Percentages were calculated excluding missing values

[†] Missing values by group (AD, DLB, VaD):

Table 2

Mean FAQ scores by time in study

Time in study (years) *	N	Mean	SD
0	5809	16.26	8.43
1	2849	19.22	8.27
2	1725	21.48	7.97
3	1000	23.21	7.29
4	502	24.68	7.03
5	117	25.07	7.03

Abbreviations: FAQ = Functional Activities Questionnaire

* Rounded to the nearest year

Table 3

Baseline differences and differences in mean FAQ annual change among AD, DLB and VaD^{*}

Model term	Model A [†]			Model B [‡]			Model C [§]		
	Estimate	95% CI	p	Estimate	95% CI	p	Estimate	95% CI	p
Baseline differences in mean FAQ[¶]									
DLB (vs. AD)	1.98	1.16, 2.81	<0.001	3.29	2.45, 4.13	<0.001	3.53	2.65, 4.42	<0.001
VaD (vs. AD)	1.30	-0.24, 2.85	0.10	1.03	-0.30, 2.35	0.13	1.22	-0.11, 2.54	0.07
VaD (vs. DLB)	-0.68	-2.40, 1.04	0.44	-2.27	-3.87, -0.66	0.006	-2.32	-4.09, -0.54	0.01
Differences in mean FAQ annual change									
DLB (vs. AD)	-0.47	-1.00, 0.05	0.08	-0.31	-0.81, 0.19	0.23	-0.35	-1.03, 0.32	0.30
VaD (vs. AD)	-1.37	-2.58, -0.16	0.03	-0.91	-1.68, -0.14	0.02	-1.51	-2.60, -0.41	0.007
VaD (vs. DLB)	-0.89	-2.20, 0.41	0.18	-0.61	-1.45, 0.24	0.16	-1.15	-2.36, 0.05	0.06

Abbreviations: AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; VaD = Vascular dementia; FAQ = Functional Activities Questionnaire

^{*}From multiple linear regression models that accounted for clustering at the center- and participant-level using Generalized Estimating Equations.

[†]Model A is the unadjusted model (n = 5,848 participants and 12,002 visits)

[‡]Model B is the multivariable model that adjusted for age, sex, race, marital status, education, co-morbidity score, years since symptom onset, Mini-Mental State Examination score, age × time, and used multiple imputation for all covariates with missing data (n = 5,848 participants and 12,002 visits)

[§]Model C was derived from Model B but excluded 1,225 participants (2,456 visits) who had at least one of the following at their study-first visit: vitamin B12 deficiency, thyroid disease, alcohol abuse, other substance abuse, other major psychiatric illness, hydrocephalus, traumatic brain injury or central nervous system neoplasm

[¶]In models B and C, inclusion of age × group interaction terms impacts interpretation of baseline differences in mean FAQ. These results should be interpreted for a 77-year old (mean age in sample)

Interpretation: negative values indicate slower FAQ annual rate of change in the first diagnostic group (compared to the reference group listed in parentheses).