Body mass index trajectories and associations with cognitive decline in people with Lewy body dementia and Alzheimer's disease

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Abstract

Background and Aims: In older adults with dementia, low body mass index (BMI) is associated with higher mortality and other adverse health outcomes. BMI or nutritional status trajectories from diagnosis have not yet been well described in dementia, especially in people with Lewy body dementia (LBD); a group that has a poorer prognosis. With this study, we aimed to evaluate the BMI trajectory in people diagnosed with mild LBD and Alzheimer's disease (AD).

Methods: The Dementia Study of Western Norway is a cohort study with annual assessments. Five-year measurements of BMI from 196 patients (LBD = 85 and AD = 111) diagnosed with mild dementia were analyzed using adjusted linear mixed-effects models.

Results: There were no differences between LBD and AD in baseline BMI, age, or mini-mental status examination (MMSE). During the follow-up, we observed a significant decrease in BMI in the LBD group across the study period (estimation [Est.]: −0.63, SE: 0.14; p < 0.001). By contrast, there was no significant change in BMI trajectory associated with AD diagnosis (Est.: 0.05, SE: 0.15; p = 0.730). Further, the introduction of an interaction term between diagnosis and time in the study showed that this difference (BMI trajectories) was significant (Est.: −0.63, SE: 0.14; p < 0.001). In addition, there was a significant interaction between MMSE total score and the follow-up time; the lower the MMSE, the lower the BMI (Est.: 0.01, SE: 0.01; p = 0.044).

Conclusion: In LBD, BMI significantly decreased with disease progression. In addition, low cognitive performance was associated with a reduction in BMI. These results highlight the importance of BMI evaluation in people with dementia, particularly patients diagnosed with LBD, and suggest that patients with LBD could be targeted for dietary intervention to maintain body weight.

KEYWORDS
Alzheimer's disease, body mass index, dementia, Lewy body dementia, malnutrition
1 | INTRODUCTION

High body weight in middle age has been associated with adverse health outcomes and increased mortality. However, in older people, low body mass index (BMI) represents a risk factor for all-cause mortality, and this effect is even more pronounced in dementia. Previous results from our group suggest that malnutrition at the time of mild dementia diagnosis and during the dementia course is associated with reduced functional performance and increased mortality.

Dementia, chronic diseases, and geriatric syndromes might contribute to weight reduction due to mechanisms such as increased energy demand and inflammation. Inflammation has several metabolic effects, including reduction of appetite and increase in insulin resistance leading to suboptimal nutrition entering the cells. Reduced nutritional body reserves impair the response to external stressors, leading to higher vulnerability and increased risk of adverse outcomes. In addition, food intake in older adults with dementia is commonly reduced due to several factors. These include age-related changes in the digestive system, loss of appetite, dysphagia, neuropsychiatric symptoms (NPS) such as depression or apathy, antidepressant drugs, economic difficulties, and loss of independence.

Clinical variability between different types of dementia needs to be considered when examining the complex interactions of weight loss and specific outcomes in this population. People with Lewy body dementia (LBD) have a higher risk of malnutrition compared to healthy controls and people with Alzheimer’s disease (AD). The latter could be an important factor contributing to the poorer prognosis of LBD patients when compared to other causes of dementia.

Few longitudinal studies of body weight in people with dementia are available in current literature, and studies focusing on LBD are lacking. This is important since strategies and interventions to maintain body weight can potentially improve the prognosis and quality of life in this population.

Here, we aimed to evaluate and compare the BMI trajectory during 5 years in older people newly diagnosed with LBD and AD.

2 | MATERIALS AND METHODS

2.1 | Setting and participants

“The Dementia Study of Western Norway” (DemVest) is a prospective multicentre cohort study of patients referred to dementia clinics in the western region of Norway (Hordaland and Rogaland counties). To reduce referral bias, general practitioners were encouraged to refer any patient with suspected dementia. The period of recruitment was between 2005 and 2013. Patients with mild dementia, defined as a mini-mental status examination (MMSE) score greater or equal to 20, or clinical dementia rating global score equal to 1 were included. Exclusion criteria at study entry were moderate or severe dementia, delirium, previous bipolar or psychotic disorder, terminal illness, or a recently diagnosed major somatic disease which could significantly impact cognition, function, or study participation. Comprehensive annual assessments were carried out. Detailed clinical assessments were conducted at baseline and then annually until death or study withdrawal. At baseline, the DemVest participants lived at home, but during follow-up, 64% of them were admitted to nursing homes. Dropout of participants resulted mainly from death, with very few lost to follow-up or withdrawal. More details of the DemVest study are provided elsewhere.

In this secondary analysis of the DemVest original cohort (n = 223), we included 196 patients with LBD or AD with complete anthropometric data at baseline. The number of participants with available anthropometric information varied at each assessment due to the retrospective nature of this secondary analysis. Data from the first five annual follow-ups of the DemVest study was used for the current analysis. All patients with the baseline were included in the analysis.

2.2 | Assessments

2.2.1 | Dementia diagnosis

Diagnosis of dementia was made according to the established criteria of the DSM-IV-TR. Specific types of dementia were diagnosed according to the corresponding validated clinical criteria. Pathological diagnosis is available in 56 subjects of the DemVest cohort, with an accuracy above 80% when compared to the clinical criteria. The final diagnosis, used for the current analysis, was determined through the consensus of a group of clinical specialists in neurology, psychiatry, and geriatric medicine, and neuropathological confirmation when available. In the current study, we included people diagnosed with AD (n = 111) and LBD (n = 85). Dementia with Lewy bodies (DLBs) (n = 70) and Parkinson’s disease dementia (PDD) (n = 15) patients were combined in one LBD group considering the similarity in genetics, neuropathology, clinical features, and management between PDD and DLB.

2.2.2 | Body mass index

BMI (at baseline and every 12 months during five follow-ups) was used as the outcome variable. Bodyweight and height were measured with the patient wearing light indoor clothing. BMI was based on objective body weight and height and calculated using the formula \( \text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2} \). For this analysis, we used BMI as a continuous variable.

2.2.3 | Confounding variables

We included demographic factors such as gender and age as potential confounders, as well as NPS, evaluated with the total score...
of the neuropsychiatric inventory (NPI), comorbidities using the Cumulative Illness Rating Scale (CIRS) based on patient and informant reports and medical record, and global cognitive performance based on the score of the MMSE in its validated Norwegian version.

2.3 | Statistical analysis

A descriptive analysis was performed by estimating percentages for categorical variables and means and standard deviations for quantitative variables. We also evaluated the differences between the diagnostic groups (i.e., LBD vs. AD) using Pearson’s $\chi^2$ test for categorical variables and independent samples Student’s $t$-test for quantitative variables.

To evaluate the group (LBD and AD) longitudinal trajectories of BMI over five assessments, we used a linear mixed-effects model with random intercept and slope and an unstructured variance–covariance matrix. BMI was used as the dependent variable in this model, and the time of follow-up was included as the independent variable. The model was further adjusted for covariates including age, sex, CIRS, and MMSE total score to control for potential confounding effects. The model included interactions between the diagnostic groups and the follow-up time to evaluate BMI trajectory in LBD and AD separately; the diagnostic groups and the CIRS and the MMSE total score with the follow-up time. The total score of NPI, and its interactions, as well as the interaction between the MMSE and the diagnostic groups, were considered but not included in the final model due to nonsignificance. We explored a nonlinear outcome association; however, it was nonsignificant.

We considered significance at $p < 0.05$ to evaluate the variables in the model. R software version 4.0.5 was used to perform all statistical analyses.

### Table 1 | Baseline characteristics

|                | AD n (%) or mean ± SD | LBD | Total | p Value |
|----------------|-----------------------|-----|-------|---------|
| Total BL       | 103 (58.19)           | 74  (41.81) | 177 (100.00) | -       |
| BMI            | 23.91 ± 4.15          | 24.91 ± 4.32 | 24.33 ± 4.24 | 0.122   |
| MMSE           | 23.61 ± 2.32          | 23.76 ± 3.17 | 23.67 ± 2.72 | 0.690   |
| NPI            | 16.03 ± 16.77         | 23.53 ± 18.68 | 19.29 ± 17.97 | 0.004   |
| Follow-up time | 4.27 ± 1.38           | 3.41 ± 1.50  | 3.91 ± 1.49  | <0.001  |
| Age            | 75.31 ± 7.52          | 75.22 ± 6.50 | 75.27 ± 7.09 | 0.937   |
| Gender         |                       |     |       |         |
| Male           | 26 (25.24)            | 43  (58.11) | 69 (38.98) | <0.001  |
| Female         | 77 (74.76)            | 31  (41.89) | 108 (61.02) | -       |
| CIRS           | 5.41 ± 2.40           | 6.67 ± 2.48  | 5.89 ± 2.50  | 0.002   |

Abbreviations: AD, Alzheimer’s disease; BMI, body mass index; CIRS, Cumulative Illness Rating Scale; LBD, Lewy body dementia; MMSE, mini-mental status examination; NPI, neuropsychiatric inventory; SD, standard deviation.

3 | RESULTS

Demographic and clinical characteristics are shown in Table 1. In the LBD group, we found a majority of male participants (LBD 58.11% vs. AD 25.24%; $p < 0.001$), the CIRS scores were also higher (LBD $6.67 ± 2.48$ vs. AD $5.41 ± 2.40$; $p = 0.002$). The mean follow-up time in the LBD group was significantly shorter ($3.41 ± 1.50$ years vs. AD $4.27 ± 1.38$ years; $p < 0.001$). There were no differences between LBD and AD regarding baseline BMI, age, or MMSE.

There was a significant interaction between the MMSE longitudinal total score and the follow-up time; the lower the MMSE, the lower the BMI (estimation [Est.]: $0.01$, SE: $0.01$; $p = 0.044$; Figure 1A).

AD participants had a lower BMI than the LBD group (Est.: $4.19$, SE: $1.76$; $p = 0.019$). However, during follow-up, there was a significant decrease of BMI in the LBD group (Est.: $-0.63$, SE: $0.14$; $p < 0.001$), but no significant change in those with AD (Est.: $0.05$, SE: $0.15$; $p = 0.730$). The $p$-value of the time × diagnosis interaction was <0.001 (see Figure 1B, Table 2).

Finally, to test the goodness of fit in our model, we compared the observed BMI with the estimated BMI results of our model. As depicted in Appendix A, there is a good correlation between the observed and the estimated BMI, reflecting a high congruency in the BMI estimations of our model for both LBD and AD subgroups.

4 | DISCUSSION

We found that BMI decreases with disease progression in those diagnosed with LBD. By contrast, AD diagnosis did not significantly explain the decline in BMI. In addition, poorer cognitive status was associated with lower BMI over time in people with mild dementia. These results highlight the importance of BMI evaluation in people living with dementia, particularly in patients with LBD.
The reduction of BMI seems to play an important role for several prognostic outcomes in older adults. Kivimäki et al.\textsuperscript{15} showed that higher BMI was associated with lower mortality risk after 85 years of age. It has been shown that malnourished people with dementia have a higher risk of mortality and functional loss.\textsuperscript{3,16} In addition, Cumming et al.\textsuperscript{17} reported that early weight loss in people with parkinsonism increased the risk of dependency, dementia, and death.\textsuperscript{18} People diagnosed with DLB are potentially more likely to have lower BMI, as well as to develop malnutrition compared to individuals without dementia and or with other types of dementia. In addition, according to other studies, markers of nutrition such as serum albumin and hemoglobin are lower among people with DLB compared with those with AD.\textsuperscript{19} In people with parkinsonism, similar findings have been described.\textsuperscript{17} We highlight that in this study, we found that LBD and AD were comparable in mild disease but that there was a substantial weight loss with disease progression in LBD.

Alongside, the more rapid decline of BMI in LBD may be related to the more complex clinical symptoms compared to AD, including motor symptoms, autonomic and sleep disturbances, NPSs, polypharmacy, comorbidity, and functional loss which may increase the barriers to locomotion, food access, purchase, and cooking.\textsuperscript{20} This may also increase catabolism, systemic inflammation and also reduce the body’s nutritional reserves.\textsuperscript{21} Additionally, swallowing disorders are highly prevalent in LBD (up to 92%), requiring LBD patients to change food consistency which may lead to a poorly balanced diet and malnutrition.\textsuperscript{18} Several reasons can be linked with a more pronounced nutritional deterioration in people diagnosed with LBD. LBD patients have a faster functional decline and receive more medications, which can be associated with the greater comorbidity and frailty present in this group.\textsuperscript{22} According to previous research by our group, frailty is more frequent in DLB 37.14% compared to AD 18.97%.\textsuperscript{23} Research has shown that polypharmacy has been associated with malnutrition and loss of weight.\textsuperscript{24} In addition, we have reported that from diagnosis to Year 5 the number of medications in LBD is significantly higher compared with LBD.\textsuperscript{25}

People with AD did not show the same BMI tendency as LBD, however, this might be associated with a slower disease progression in the initial stages. In addition, AD is more widely known among clinicians, thus it might be possible that people diagnosed with AD had a better trajectory due to better identification and treatment. However, all the participants were selected carefully with the inclusion criteria for mild dementia and treated using current standard guidelines independently of their diagnosis.

This study has several strengths, including the long follow-up time and annual assessments with structured validated instruments.

### TABLE 2

|                | Unadjusted model |                    | Adjusted model |                    |
|----------------|------------------|--------------------|----------------|--------------------|
|                | Est.             | Std. err.          | p Value        | Est.             | Std. err.          | p Value        |
| Intercept      | 24.33            | 0.32               | <0.001         | 27.17            | 3.26               | <0.001         |
| Time           | −0.13            | 0.08               | 0.077          | 0.05             | 0.15               | 0.730          |
| Group          |                  |                    |                |                  |                    |                |
| LBD            | −4.19            | 1.76               | 0.019          |                  |                    |                |
| Age            | −0.63            | 0.14               | <0.001         |                  |                    |                |
| Gender         |                  |                    |                |                  |                    |                |
| Female         | −0.44            | 0.68               | 0.519          |                  |                    |                |
| CIRS           | −0.57            | 0.17               | <0.001         |                  |                    |                |
| LBD            | −0.60            | 0.26               | 0.022          |                  |                    |                |
| MMSE           | 0.01             | 0.02               | 0.706          |                  |                    |                |
| Time           | 0.01             | 0.01               | 0.044          |                  |                    |                |

Abbreviations: AD, Alzheimer’s disease; BMI, body mass index; CIRS, Cumulative Illness Rating Scale; Est., estimation; LBD, Lewy body dementia; MMSE, mini-mental state examination.

Continuous variables were scaled with z-score transformation.
from the time of dementia diagnosis. The latter allowed assessment from mild to severe dementia. Also, diagnostic procedures were rigorous and highly accurate; the neuropathological diagnosis was available in a subgroup demonstrating that the clinical diagnoses were accurate. Previous research by our group has shown that being overweight at the time of mild dementia diagnosis was associated with better cognitive performance across dementia progression. This also supports our current findings, where cognitive performance had a significant association with BMI.

Among the limitations of the study is a potential recruitment bias because of referrals of primary care patients, which may have led to an increased number of patients with complicated dementia or poorer health status. However, general practitioners were invited to refer any patient with suspected dementia. Patients were treated according to recommendations for pharmacological and nonpharmacological interventions which may influence the course of the disease and thus also mortality. In addition, several medications frequently prescribed in people with dementia have been associated with gastrointestinal complaints and anorexia, which could affect food intake and body weight. This is particularly important in LBD patients who have more comorbidities and motor and nonmotor manifestations. There was a significantly lower number of males in the AD group, which could have biased the results, therefore adjustments by sex were included in all the models. After the fifth year, there was a considerable number of dropouts and missing values in the cohort, which did not allow us to evaluate the progression of AD subjects after that time. In addition, due to the small sample, we did not differentiate DLB from PDD. It is possible that the more severe parkinsonism in PDD may cause a more severe weight loss. Blood samples were available only at baseline in a limited number of patients, nutritional markers such as albumin, for example, should be considered in further studies. This study involved data analyzed after the DemVest cohort recruitment and 5-year annual follow-up has been concluded, thus not controlled multifactorial factors could also explain our results. However, careful consideration of confounding factors and a statistical approach were considered to reduce these biases. Generally, it has been reported that BMI allows good approximations of body composition, nutritional status, and specifically changes associated with adipose tissue. Despite the above benefits of BMI, there are several considerations when evaluating this measure. It is important to highlight that the BMI in older adults can be susceptible to bias due to age-related physiological changes, and moreover in people with increased prevalence of chronic diseases. Other approaches such as using weight loss only, have also been shown to be useful in cardiovascular patients where the "obesity paradox" was observed. However, BMI is a more frequently used method allowing comparing with other studies and management guidelines that base their methods and recommendations on the BMI.

This study elucidates the importance of calculating BMI as a marker of nutrition, especially in people with LBD. Calculating BMI is an easy, inexpensive, and accessible measure. Therefore, we suggest that BMI evaluation in clinical practice may provide additional information regarding treatment and interventions that might improve prognosis in patients with dementia, especially those diagnosed with LBD. Interventions such as nutritional programs or protein-calorie supplementation have been shown to be effective in older persons living with frailty and or dementia, and also physical activity, and deprescription of unnecessary medications. Thus, maintenance of adequate weight and nutrition could represent a possible treatment opportunity in patients with LBD.

In conclusion, we found that people diagnosed with LBD lose BMI during the progression of the disease and that this was associated with cognitive decline. This is important due to the negative prognostic consequences of malnutrition and the potential for interventions to improve nutrition and possibly also prognosis. Further research is needed to replicate our findings, to explore the prognostic effects of malnutrition, and, most importantly, to conduct intervention trials to improve nutrition and possibly improve the prognosis of people with LBD (Figure A1).

AUTHOR CONTRIBUTIONS
Study concept and design, interpretation of data, and preparation of the manuscript: Miguel G. Borda. Study concept and design, analysis and interpretation of data, and preparation of the manuscript: Lasse M. Gil. Analysis and interpretation of data, and preparation of the manuscript: Diego Alejandro Tovar-Rios. Interpretation of data, and preparation of the manuscript: Alberto Jaramillo-Jimenez. Interpretation of data, preparation of the manuscript, and supervision: Hogne Soennesyn. Study concept and design, interpretation of data, preparation of the manuscript, and supervision: Dag Aarsland. All authors have read and approved the final version of the manuscript and had full access to all the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

TRANSPARENCY STATEMENT
The lead authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.
DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT
This study was approved by the regional ethics committee (approval code: 2010/633) and the Norwegian authorities for the collection of medical data. All data were handled and kept following national health and data privacy protocols. All participants signed an informed consent form before inclusion in the study.

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APPENDIX A

**FIGURE A1**  Goodness of fit of the adjusted model for BMI trajectories. AD, Alzheimer’s disease; BMI, body mass index; LBD, Lewy body dementia.