Cognitive-Driven Activities of Daily Living Impairment as a Predictor for Dementia in Parkinson Disease

A Longitudinal Cohort Study

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Abstract

Background and Objectives
One-third of Parkinson disease (PD) patients with PD-mild cognitive impairment (PD-MCI) convert to dementia within a few years. Markers with a high prognostic value for dementia conversion are needed. Loss of everyday function primarily caused by cognitive dysfunction is the core criterion for the diagnosis of PD dementia, with an onset of more complex instrumental activities of daily living (IADL) dysfunction in the prodromal stage. This study evaluated the phenotype associated with cognitive IADL impairment and its predictive value for defining a high-risk group for PD dementia.

Methods
An observational longitudinal study using cognitive and clinical scores in addition to genetic and CSF biomarkers was conducted. The Functional Activities Questionnaire quotient (cut-off ≥1), indicating more cognitive than motor-driven IADL impairment, defined cognitive IADL impairment status at baseline. Hazard ratios (HRs) were used to compare the impact of baseline classifications on dementia conversion.

Results
Of 268 patients with PD assessed at baseline, 108 (40.3%) had PD-MCI. After a period of 3.78 ± 0.84 years, 164 (61.2%) patients were reassessed. At follow-up, 93 (56.7%) patients had no cognitive impairment, 54 (32.9%) fulfilled PD-MCI criteria, and 17 (10.4%) had developed dementia. The HR of baseline cognitive IADL impairment (n = 37) for dementia conversion was descriptively higher than for PD-MCI, but highest in patients with both markers (HR = 12.01, 95% CI 4.47–32.22, $p < 0.001$). In the follow-up sample, nearly half of the patients (n = 10, 47.6%) with baseline classification of cognitive IADL impairment and PD-MCI converted to dementia. Baseline status of cognitive IADL impairment was associated with higher nonmotor burden, worse cognitive performance, and more severe IADL progression over the study period.

Discussion
The importance of differentiating between cognitive and motor aspects on ADL function in PD and monitoring cognitive ADL impairment in the prodromal stage of dementia is paramount. Patients with PD-MCI and cognitive IADL impairment may be a valuable target group for clinical trials aiming to slow down the development of dementia.

Trial Registration Information
ClinicalTrials.gov NCT03687203.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Glossary

ADL = activities of daily living; **BDI-II** = Beck Depression Inventory-II; **FAQ** = Functional Activities Questionnaire; **GLMM** = Generalized linear-mixed effects model; **HR** = hazard ratios; **IADL** = instrumental ADL; **MDS** = Movement Disorder Society; **NMSQ** = Nonmotor Symptoms Questionnaire; **OR** = odds ratio; **PD** = Parkinson disease; **PD-CN** = PD Cognitively Normal; **PDD** = PD Dementia; **PD-MCI** = PD With Mild Cognitive Impairment; **ROC** = reciever operating characteristic; **UPDRS** = Unified Parkinson Disease Rating Scale.

Classification of Evidence

This study provides Class II evidence that impairment of cognitive activities of daily living is associated with progression from MCI to dementia among patients with Parkinson disease.

Patients with Parkinson disease (PD) have an almost 6-fold increased risk of developing cognitive impairment and Parkinson Disease Dementia (PDD) compared with age-matched controls.[1] Identification of a high-risk group for those converting to PDD (i.e., those who are in the prodromal dementia phase) is essential to develop and implement early and effective treatments for preventing or delaying dementia. PD with mild cognitive impairment (PD-MCI) is one of the greatest risk factors for future PDD.[2] A recent meta-analysis found that, on average, 31% of patients with PD-MCI converted to PDD within 7 years; however, 24% of patients with PD-MCI reverted back to normal cognitive function.[3] Consequently, the false-positive rate for predicting PDD among patients with PD-MCI is high, and better predictive markers to define patients at high risk for PDD development are urgently needed.

The fundamental feature differentiating PDD from PD-MCI is the loss of the ability to perform activities of daily living (ADL),[4] which can be divided into basic ADL (e.g., dressing or bathing) and instrumental ADL (IADL, e.g., shopping or managing medication).[5] Although basic ADL skills are generally preserved longer during the disease course, the more complex IADL skills can be impaired even in early stages of cognitive decline.[6] IADL impairment assessed by various measures (e.g., questionnaires and objective tests) can be observed in approximately 30%–50% of patients with PD-MCI,[7,8] suggesting that cognition affects IADL even in the prodromal stage of PDD. To date, studies suggest that progression of IADL is associated with worsening of some cognitive measures and future cognitive test performance, but with inconclusive results for predicting cognitive diagnosis because of a scarcity of longitudinal studies.[6,9]

On a cross-sectional level, not all studies confirm a direct link between cognition and function in PD,[10,11] implying that not all instruments are suitable for detecting cognitive-driven IADL and might be confounded by other noncognitive effects. It is of importance that the impairments in daily function necessary to define PDD must be primarily caused by cognitive deficits, mainly reflecting deficits in IADL.[1,12]

However, motor impairments can also affect IADL ratings,[13,14] highlighting the challenge of identifying impairments indicative of dementia in patients with PD. To overcome this obstacle, research has focused on creating new comprehensive instruments, such as the Penn Parkinson Daily Activities Questionnaire.[15] A recent study developed novel subscores using the Functional Activities Questionnaire (FAQ) to differentiate cognitive and motor contributions to IADL impairment in patients with PD without dementia by examining associations between each FAQ item and a measure of global cognition (to create the cognition subscore) and a measure of motor severity (to create the motor subscore).[16] A quotient (FAQ_Q) was calculated by dividing the cognitive by the motor subscore, to define a subgroup of patients with more cognitive compared with motor-driven IADL impairment. Further analyses revealed that this group scored lower on attention and language tests, suggesting more advanced cognitive deterioration in patients with cognitive IADL dysfunction.[16]

Based on these previous results, the main goal of this study was to examine cognition and IADL function in a longitudinal PD cohort. The primary research aim (1) was to evaluate whether patients with cognitive IADL impairment, defined according to the FAQ_Q (cut-off >1), are at higher risk for the development of PDD and to determine whether the combination of PD-MCI and cognitive IADL impairment better predicts conversion to PDD than either marker alone. We hypothesized that patients with both PD-MCI and cognitive IADL impairment are at a higher risk for conversion to PDD than patients with motor IADL impairment. The following secondary research aims were addressed (2) to define the baseline phenotype associated with cognitive IADL impairment, expecting a profile of lowered cognitive performance and higher rate of genetic risk variants and CSF biomarkers related to impaired cognition and (3) to investigate progression in function over time reflected by change in the FAQ subscores hypothesizing that patients with either a baseline classification of PD-MCI or cognitive IADL impairment would have higher values in the FAQ subscores at the follow-up.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Both studies were approved by the Ethics Committee of the Medical Faculty of the University of Tübingen (Baseline 686/2013BO1; Follow-up 284/2018BO1). The follow-up study was registered at ClinicalTrials.gov, Identifier: NCT03687203. Written informed consent was obtained from patients or a proxy (if necessary) for both studies and additionally from informants for the follow-up study.

Design and Recruitment

Baseline visit was conducted between March 2014 and December 2017 within the frame of the single-site "Amyloid-Beta in cerebrospinal spinal fluid as a risk factor for cognitive dysfunction in Parkinson Disease" (ABC-PD) study. Patients with PD were recruited from a movement disorders population through the Neurology Department of the University Hospital in Tübingen and regional neurologists and assessed in-house. Patients were included if they were fluent German speakers, were aged 50–85 years, were able to give informed consent, had a diagnosis of PD according to the UK Brain Bank criteria, had no concomitant neurologic diseases affecting cognition (stroke, traumatic brain injury, and encephalitis) or diagnosis of PDD, had no Deep Brain Stimulation, and agreed to a lumbar puncture.[16]

The follow-up visit was conducted using the "Cognitive-driven ADL impairment as a predictor for Parkinson disease dementia" study. Between July 2018 and September 2020, all patients of the ABC-PD study were contacted for re-examination. Inclusion criteria for follow-up participation were age between 50-90 years and ability to communicate with the investigator and understand the purpose of this study. Patients with concomitant diseases affecting cognition or who had received a neurologic diagnosis other than PD between visits were excluded. Medical history was obtained through detailed anamnesis at both visits and a thorough review of hospital medical records to identify concomitant diseases or other neurologic diagnoses. Because long-term effects of Deep Brain Stimulation on ADL are unclear, these patients were excluded from analyses. Assessments took place either in-house or at patients' homes. Minimal assessments, where relevant medical records and ADL questionnaires were obtained from patients or caregivers, were conducted if patients were too impaired for neuropsychological testing. Figure 1 shows a detailed recruitment flowchart.

Assessments and Outcomes

Demographics (age, sex, formal education, and age at disease onset) were collected at baseline; all clinical variables were assessed at both visits. The motor part of the Movement Disorder Society (MDS) Unified Parkinson Disease Rating Scale (MDS-UPDRS-III) and Hoehn & Yahr scale assessed severity of motor symptoms.[17] Antiparkinsonian medication intake was expressed using the levodopa equivalent daily dose. German versions of the Nonmotor Symptoms Questionnaire (NMSQ)[18] and the Beck Depression Inventory-II (BDI-II)[19] measured nonmotor symptom burden. These baseline variables were considered as potential between-group covariates.

IADL: The 10-item FAQ assessed IADL (see eTable 1 for item descriptions and scoring, links.lww.com/WNL/C307). The FAQ total score (0–30 points) was calculated, and the following novel subscores[16] were defined: FAQ cognition score—primarily associated with cognitive aspects (items 1, 2, 7, 8, and 9), FAQ motor score—primarily associated with motor aspects (items 3, 4, 5, 6, 7, 8, and 10), and the FAQ quotient $[FAQ_Q=(FAQ \text{ cognition score } +1)/(FAQ \text{ motor score } +1)]$. A cut-off score >1 on the FAQ_Q, indicating more cognitive compared with motor-driven IADL impairment, was used to differentiate patients with more cognitive ($FAQ_{Q>1}$) from more motor ($FAQ_{Q\leq1}$) IADL impairment.[16] Progression in function over time was reported for the FAQ total, FAQ cognition, FAQ motor, and FAQ_Q scores. At baseline, the FAQ was completed by either an informant or the patient themselves if no informant was available; the follow-up FAQ data were obtained from the same source as the baseline data.

Cognition: Patients underwent comprehensive neuropsychological testing at both visits that has been described in detail elsewhere.[16] In short, the Consortium to Establish a Registry for Alzheimer Disease–Plus Battery,[20] 3 subtests from the Wechsler Intelligenztest für Erwachsene (German version of the Wechsler intelligence test for adults)[21] and 1 subtest from the "Leistungsprüfsystem 50+" (LPS50+; cognitive test battery for adults 50 years or older)[22] were used. The Montreal Cognitive Assessment measured global cognitive functioning.[23] Raw scores were converted to age-corrected or age- corrected and education-corrected z-scores, and composite domain scores (attention, executive functions, memory, visuospatial abilities, and language) were calculated from respective z-scores (Table 1). Patients were classified as PD-MCI according to level-II MDS recommendations if cognitive impairment (performance on at least 2 tests below 1.5 standard deviations of the population mean reported in the test manuals) was present but did not significantly interfere with everyday function.[24] PDD was defined according to MDS Task Force criteria[4] if cognitive impairment was present and severe enough to impair ADL function unrelated to motor or autonomic symptoms, and at least one behavioral symptom was present to support diagnosis. Cognitive impairment was defined according to Level-I (impairment of global cognition) for patients with minimal assessments or Level-II (performance on at least 2 tests below 1.5 standard deviation of the population mean reported in the test manuals) for patients assessed using a full cognitive battery. Patients not meeting either of the diagnostic criteria were classified as PD cognitively normal (PD-CN). Cognitive status at the follow-up was defined as the primary study outcome.

Genetics and biomarkers: Genetic variants and CSF biomarkers were derived from baseline samples. Owing to confounding factors, CSF values were indeterminable for 1 patient. CSF $A\beta_{1-42}$, total tau, and phosphorylated tau levels were determined using

Figure 1 Flowchart of Patient Recruitment Including Cognitive Diagnosis at Follow-up
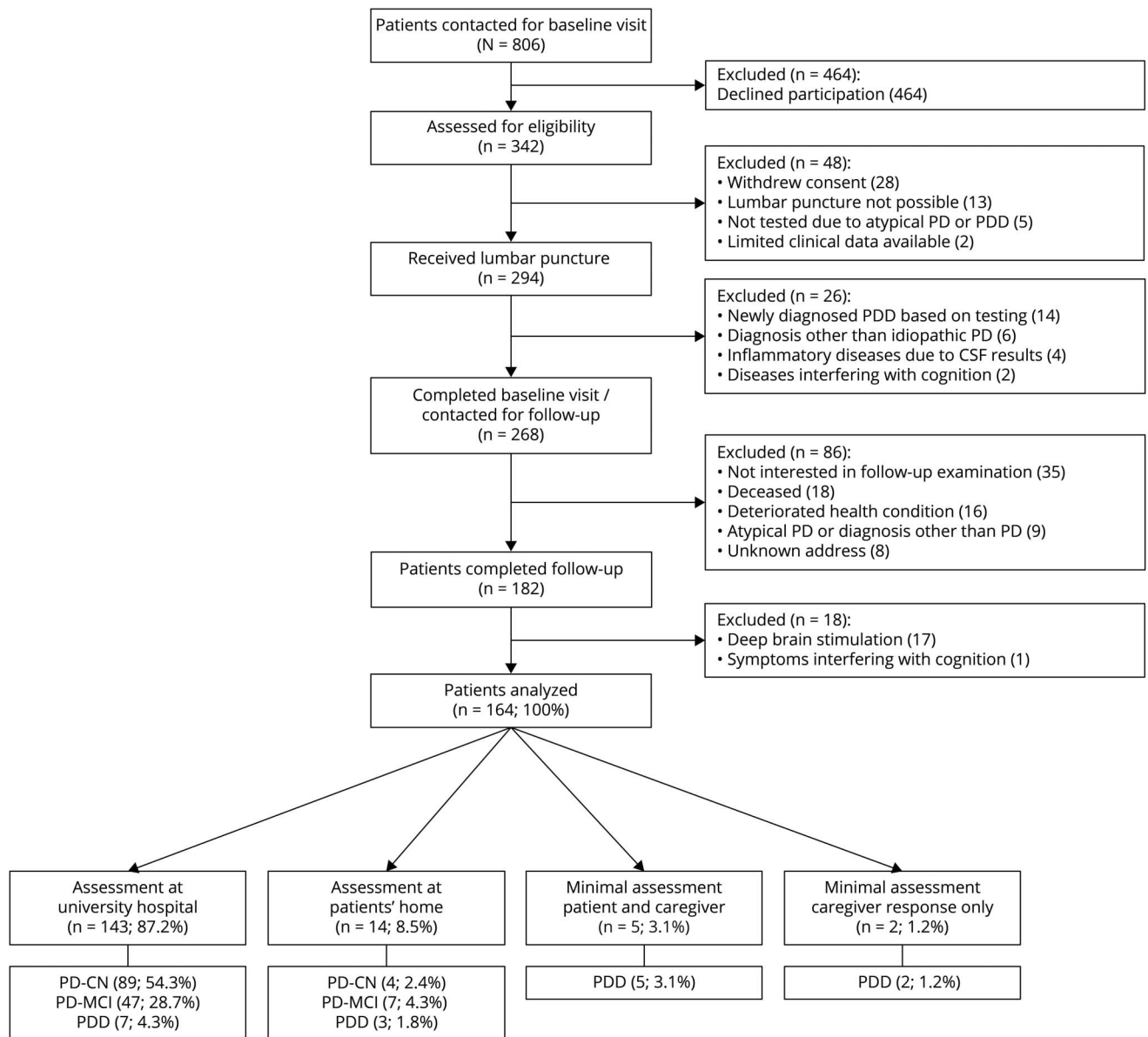
Abbreviations: FU = follow-up; PD = Parkinson disease; PD-CN = Parkinson's Disease Cognitively Normal; PDD = Parkinson Disease Dementia; PD-MCI = Parkinson Disease with Mild Cognitive Impairment.

commercially available ELISA kits (Fujirebio Europe, Gent, Belgium). Genotyping with the NeuroChip was conducted. Based on a literature review of cognitive worsening in PD and/or neurodegeneration, 10 candidate genetic variants in the genes *APOE, MAPT, SNCA, TREM2, BDNF, DYRK1A,* and *COMT*, as well as carrier status of rare *GBA* sequence variants, were selected for analysis in a hypothesis-driven approach. GBA sequence variants (c.115+1G>A, R78C(R39C), T336S(T297S), E365K(E326K), R398*(R359X), T408M(T369M), N409S(N370S), and L483P(L444P) were determined by using Sanger sequencing.

Statistical Analyses

All data were collected and managed using REDCap electronic data capture tools hosted at the Hertie Institute for Clinical Brain

Research.[25] Analyses were run using R (R Foundation for Statistical Computing, Vienna, Austria[26]) and IBM SPSS Statistics for Windows version 27 (IBM Corp., Armonk, NY). Alpha was set to 0.05; the Shapiro-Wilk test was applied to test for normal distribution. Continuous predictors were standardized in linear models. No corrections for multiple testing were applied for the characterization of study groups to be able to identify covariates for the outcome analyses.

Between-group comparisons at both visits were conducted using Mann-Whitney U or Welch tests (2 groups) or Jonckheere-Terpstra tests (>2 groups, R package "clinfun," version 1.0.15, 1,000 permutations) for numerical variables and χ^2 tests or Fisher exact test for categorical variables.

Table 1 Baseline Characterization of Patients With Cognitive (FAQ$_{Q>1}$) and Motor (FAQ$_{Q \leq 1}$) IADL Impairment

	Total cohort	FAQ$_{Q \leq 1}$	FAQ$_{Q>1}$	*p* Value
N/%	268/100	204/76.1	64/23.9	
Demographics				
Male sex, n/%	168/62.7	126/61.8	42/65.6	0.68
Age yr.	66.2/13.4	66.3/14.1	65.9/11.1	0.90
Education yr.	13/4	13/4	12/4	0.07
Age at onset yr.	60.9/14.9	61.1/14.2	60.7/12.1	0.90
Disease duration yr.	4.1/5.7	4.0/5.2	4.4/6.7	0.59
Levodopa equivalent daily dose	511/515	508/517	555/446	0.44
Motor and nonmotor scales				
MDS-UPDRS-III	25/16	25/15	26/16	0.89
Hoehn & Yahr, n/%				0.81
1	35/13.1	26/12.8	9/14.1	
2	152/56.7	118/57.8	34/53.1	
3	78/29.1	58/28.4	20/31.3	
4	3/1.1	2/0.9	1/1.6	
Beck Depression Inventory-II	7/8	6/7	9/10	**0.002**
Nonmotor Symptoms Questionnaire	7/6	7/6	10/8	**<0.001**
IADL				
FAQ total score	1/3	0/2	3/4	**0.002**
FAQ cognition score	0/0.07	0/0	0.13/0.13	**<0.001**
FAQ motor score	0/0.10	0/0.10	0.05/0.11	**0.68**[a]
Cognition				
Montreal Cognitive Assessment [11]	26/5	26/4	25/4	**0.01**
Attention [3]	−0.10/1.00	−0.10/0.80	−0.60/0.93	**<0.001**
Digit Symbol Test (WIE) [2]	−0.20/0.60	−0.20/0.90	−0.60/0.80	**0.015**[a]
Letter-Number Sequencing (WIE) [1]	0.00/1.40	0.00/1.40	−0.60/1.60	**<0.001**[a]
Executive functions [5]	−0.23/1.75	−0.20/1.80	−0.43/1.65	0.17[a]
Semantic fluency (CERAD-PLUS)	−0.50/1.30	−0.40/1.35	−0.55/1.16	0.26[a]
Phonemic fluency (CERAD-PLUS) [1]	0.10/1.20	0.00/1.20	−0.10/1.10	0.62[a]
Trail Making Test Part B (CERAD-PLUS) [4]	−0.30/1.90	−0.20/1.60	−0.70/1.95	**0.048**
Memory [1]	−0.30/1.28	−0.10/1.13	−0.58/1.41	**0.005**
Word List Learning (CERAD-PLUS)	−0.20/1.90	0.00/1.85	−0.70/1.78	**0.032**
Word List Recall (CERAD-PLUS)	−0.20/1.40	−0.10/1.30	−0.55/1.73	0.11[a]
Constructional Praxis Recall (CERAD-PLUS) [1]	−0.50/1.75	−0.40/1.80	−0.80/1.65	**0.024**[a]
Visuospatial Abilities	−0.50/1.35	−0.35/1.35	−0.78/1.16	0.11[a]
Constructional Praxis (CERAD-PLUS)	−0.70/2.03	−0.70/2.10	−0.70/1.95	0.50[a]
Fragmented Words (LPS 50+)	−0.40/1.50	−0.30/1.50	−0.80/1.60	**<0.001**
Language [1]	0.10/1.00	0.15/1.00	−0.23/1.30	**<0.001**[a]

Continued

	Total cohort	FAQ$_{Q \leq 1}$	FAQ$_{Q>1}$	*p* Value
Boston Naming Test (CERAD-PLUS)	0.40/1.50	0.50/1.50	−0.25/1.93	**0.008**[a]
Similarities (WIE) [1]	−0.20/1.00	0.00/1.40	−0.60/1.00	**0.001**[a]

Abbreviations: CERAD-PLUS = Consortium to Establish a Registry for Alzheimer Disease; FAQ = Functional Activities Questionnaire; FAQ$_Q$ = Functional Activities Questionnaire quotient; FAQ$_{Q>1}$ = cognitive instrumental activities of daily living impairment; FAQ$_{Q \leq 1}$ = motor instrumental activities of daily living impairment; IADL = instrumental Activities of daily living; LPS 50+ = Leistungsprüfsystem 50+; PD-CN = Parkinson Disease Cognitively Normal; PDD = Parkinson Disease Dementia; PD-MCI = Parkinson Disease with Mild Cognitive Impairment; MDS-UPDRS-III = Movement Disorder Society Unified Parkinson Disease Rating Scale part III; WIE = Wechsler Intelligenztest für Erwachsene; yr. = years.
Unless otherwise indicated, values are reported as *median/interquartile range* (IQR = Q3-Q1). Boldface denotes statistically significant values ($p < 0.05$). Missing values are reported in brackets [].
[a] Nonmotor Symptoms Questionnaire was a significant covariate ($p < 0.05$).

Comparisons of patient and informant ratings of the FAQ (items, total score, and subscores) were conducted using Fisher exact and Mann-Whitney *U* tests (eTables 1 and 2, links.lww.com/WNL/C307). Effect sizes were calculated as appropriate [Mann-Whitney *U* test: $r = \frac{Z}{\sqrt{N}}$, CIs were bootstrapped with 1,000 samples; χ^2 test and Fisher exact test: Cramer' *V*].

All of the following hypotheses were tested a priori; no post hoc corrections of *p* values were conducted. The predictive values (aim 1) of baseline IADL stratification (FAQ$_{Q \leq 1}$ vs FAQ$_{Q>1}$), cognitive status (PD-CN vs PD-MCI), and both markers combined (PD-MCI + FAQ$_{Q>1}$ vs other categories) were calculated using multivariate Cox proportional hazard models (R package "survival," version 3.2–11), correcting for covariates (characteristic variables significantly different between each cohort at baseline, see also Table 1 and eTable 3, links.lww.com/WNL/C307). To correct for selection bias, models were run using an uncensored cohort (including only patients with the follow-up data) and using a right censored cohort (including dropouts assuming an outcome of PD-CN at the time of drop-out). Akaikes information criterion (AIC) and concordance index (C-index)[27] were used as model fit indices. Survival curves were adjusted by conditionally balancing the sample across baseline covariates (R package "survminer," version 0.4.9). In the total baseline sample, available clinical, genetic, and CSF data were compared between patients with cognitive (FAQ$_{Q>1}$) and motor IADL (FAQ$_{Q \leq 1}$) impairment using logistic regression analyses and linear regression models (Wald statistics), correcting for BDI-II and NMSQ score (aim 2).

Generalized linear-mixed effects models (GLMMs) evaluated performance on the FAQ over time (aim 3). Three binomial models were calculated including FAQ total, cognition, or motor score as dependent variables modeled as proportions using La Place approximation and Wald parameter estimates (R package "lme4," version 1.1–27). Main effects of time of visit (baseline vs follow-up), baseline cognitive (PD-CN vs PD-MCI) and baseline status of cognitive IADL impairment (FAQ$_{Q \leq 1}$ vs FAQ$_{Q>1}$), and 3 lower order interactions (visit*cognitive status, visit*cognitive IADL status, and cognitive IADL status*cognitive status) were examined. To determine whether baseline FAQ$_{Q>1}$ and PD-MCI statuses

were associated with worse follow-up FAQ outcomes, a 3-way interaction (visit*cognitive IADL status*cognitive status) was included into the model. Baseline covariates (see eTable 3 for details, links.lww.com/WNL/C307) were added as main effects, and participants were included as random intercepts. Theoretical marginal R^2_M and conditional R^2_C values were calculated (R package "MuMIn," version 1.43.17). Bobyqa optimizer was used, and the FAQ total and motor score models were corrected for overdispersion.

For a post hoc exploratory analysis to identify which subscore best predicted PDD conversion, reciever operating characteristic (ROC) curves were calculated for all FAQ scores. The optimal score/cut-off was chosen according to the highest Youden Index.

Data Availability

The corresponding author will consider any requests for access to the data reported in this article (including deidentified participant data and the corresponding data dictionary). Owing to restrictions imposed by the Ethics Committee of the Medical Faculty of the University of Tübingen, data access must be in accordance with the approved patient consent procedure to protect patient privacy.

Results

Baseline Characteristics and Cognitive IADL Phenotyping

Two-hundred sixty-eight patients were enrolled at baseline; 160 (60.7%) were classified as PD-CN and 108 (40.3%) as PD-MCI. Patients were predominantly male (n = 168, 62.7%) and in mild to moderate disease stages according to the Hoehn & Yahr score (see Table 1 for cohort characteristics).

According to the a priori defined FAQ$_Q$ cut-off, 64 (23.9%) patients had cognitive IADL impairment (FAQ$_{Q>1}$) and 204 (76.1%) scored below this cut-off (FAQ$_{Q \leq 1}$). Patients with FAQ$_{Q>1}$ reported more nonmotor symptoms and depression compared with patients in the FAQ$_{Q \leq 1}$ group (Table 1). Patients in the FAQ$_{Q>1}$ group also had more impairments in most neuropsychological subtests and cognitive domains, except for

Table 2 Results of Binary Logistic Regression Analyses Comparing Baseline Genetic Variants and CSF Biomarkers Between Patients With Cognitive (FAQ$_{Q>1}$) and Motor IADL Impairment (FAQ$_{Q\leq1}$)

	FAQ$_{Q\leq1}$	FAQ$_{Q>1}$	p Value[a]	Model fit indices	β coefficient (95% CI)
N/%	203/76	64/24.0			
Genetic variants					
APOE ε4 allele carrier [24]	48/23.6	10/15.6	0.24	0.08	−0.46 (−1.23, 0.31)
MAPT H1/H1 carrier [24]	139/68.5	33/51.6	**0.009**	0.11	−0.86 (−1.50, −0.22)
SNCA rs356220 [24]			0.62	0.07	0.08 (−0.23, 0.39)
C/C	48/23.6	18/28.1			
C/T	101/49.8	25/39.1			
T/T	37/18.2	14/21.9			
SNCA rs7681440 [25]			0.51	0.07	0.10 (−0.20, 0.41)
G/G	47/23.2	14/21.9			
C/G	97/47.8	28/43.8			
C/C	41/20.2	15/23.4			
TREM2 R62H carrier [24]	6/3.0	2/3.1	0.69	0.07	0.35 (−1.32, 2.01)
BDNF V66M carrier [24]	70/34.5	22/34.4	0.85	0.07	−0.06 (−0.69, 0.57)
DYRK1A rs2835713 [24]			0.28	0.08	−0.18 (−0.51, 0.15)
A/A	126/62.1	44/68.8			
A/G	54/26.6	11/17.2			
G/G	6/3.0	2/3.1			
DYRK1A rs9974126 [24]			0.08	0.09	−0.28 (−0.61, 0.04)
G/G	84/41.4	32/50.0			
A/G	83/40.9	22/34.4			
A/A	19/9.4	3/4.7			
COMT V158M carrier [24]	56/27.6	18/28.1	0.95	0.07	0.02 (−0.64, 0.68)
COMT L136L [24]			0.47	0.07	−0.12 (−0.43, 0.20)
C/C	66/32.5	23/35.9			
C/G	87/42.9	27/42.2			
G/G	33/16.3	7/10.9			
GBA sequence variants carrier[b] [3]	22/10.8	8/12.5	0.77#	0.08	0.14 (−0.75, 1.02)
CSF markers					
Aβ$_{1-42}$ [1]	652.0/266.5	684.0/293.5	0.39#	0.09	0.13 (−0.16, 0.41)
Phosphorylated tau	226.0/129.0	242.5/104.0	0.09#	0.10	−0.29 (−0.63, 0.05)
Total Tau	40.0/20.0	40.0/16.3	0.24#	0.09	−0.20 (−0.53, 0.13)

Abbreviations: APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; COMT = catechol-O-methyltransferase; DYRK1A = dual specificity tyrosine phosphorylation regulated kinase 1; GBA = glucosylceramidase beta; MAPT = microtubule-associated protein tau; SNCA = alpha-synuclein; TREM2 = triggering receptor expressed on myeloid cells 2.

Results are expressed as n/% for genetic variants and *median/interquartile range (IQR = Q3-Q1)* for CSF markers. Boldface denotes statistically significant values ($p < 0.05$). Nagelkerke R^2 was used as the model fit index. Missing values are reported in brackets []; one patient was excluded from analyses as both genetic data and CSF markers were missing.

[a] p values were corrected for Beck Depression Inventory-III and Nonmotor Symptoms Questionnaire.

[b] Sequence variants of the *GBA* gene include c.115+1G>A, R78C(R39C), T336S(T297S), E365K(E326K), R398*(R359X), T408M(T369M), N409S(N370S), and L483P(L444P). #Nonmotor Symptoms Questionnaire was a significant covariate ($p < 0.05$).

performance on visuospatial and executive function domain scores. $FAQ_{Q>1}$ status was associated with a lower probability of carrying MAPT H1/H1 variant (odds ratio [OR], OR = 0.42, p = 0.009, 95% CI 0.22–0.80, Nagelkerke R^2 = 0.11; Table 2). The A-Allele of *DYRK1A* rs9974126 was descriptively less associated with the baseline status of $FAQ_{Q>1}$ (OR = 0.76, p = 0.08, 95% CI 0.54–1.04, Nagelkerke R^2 = 0.09). Further logistic regression analyses revealed that no CSF marker differed between patients FAQ_Q groups.

Followup Characteristics

Of the baseline cohort, 164 patients (61.2%) were reanalyzed with a mean follow-up interval of 3.78 ± 0.84 years (*range* 1.67–5.79 years). Most patients lost to follow-up were either not interested in re-examination or deceased (Figure 1). Patients lost to follow-up or excluded for analyses were older and had more depression, motor severity, cognitive impairment, and functional impairment at baseline (eTable 4, links.lww.com/WNL/C307). The number of patients with baseline status of cognitive IADL impairment was not significantly different between patients who dropped out compared with those who were included.

Regarding the primary outcome, 17 (10.4%) patients converted to PDD, with 12 (70.6%) fulfilling Level-II diagnostic criteria for PDD—2 of them between study visits without Level-II confirmation at the follow-up (minimal assessments). Four (23.5%) patients were diagnosed by a neurologist (Level-I), and one (5.9%) patient was diagnosed by a general physician. Fifty-four (32.9%) patients were classified as PD-MCI at the follow-up, with diagnosis in 31 (18.9%) patients stable across both visits, and 93 (56.7%) patients were classified as PD-CN, with 79 (48.2%) patients cognitively normal at both visits. Significant differences were found between all cognitive groups for age, education, motor severity, nonmotor symptoms, depression severity, FAQ subscores, and neuropsychological test scores (eTable 5, links.lww.com/WNL/C307).

For patients completing both visits, 90 (54.9%) FAQ scores were rated by an informant, while 74 (45.1%) patients filled out the FAQ themselves. There were no significant differences on FAQ items, total, and subscore values between patient and informant ratings (eTables 1 and 2, links.lww.com/WNL/C307). At follow-up, 37 (21.3%) patients had a baseline status of cognitive IADL impairment ($FAQ_{Q>1}$) and 127 (78.7%) patients had a baseline $FAQ_{Q\le1}$. There was no significant difference between cognitive IADL groups regarding the follow-up interval [Welch test: $t(60.65)$ = −1.67, p = 0.10; $FAQ_{Q>1}$ mean 3.68 ± 0.85 years, $FAQ_{Q\le1}$ mean 3.94 ± 0.81 years].

Prediction of PDD Conversion According to Baseline Cognitive IADL Impairment

In the follow-up (uncensored) cohort, 11 (29.7%) patients with baseline status of cognitive IADL impairment ($FAQ_{Q>1}$) converted to PDD during the study period compared with only 6 (4.7%) in the $FAQ_{Q\le1}$ group (Figure 2). In addition, 13 (22.4%) patients who had a baseline diagnosis of PD-MCI were diagnosed as PDD at the follow-up. Of 21 with baseline PD-MCI and

cognitive IADL impairment ($FAQ_{Q>1}$), 10 (47.6%) progressed to PDD during the study period. By contrast, only 3 patients (8.1%) classified as PD-MCI with motor IADL impairment ($FAQ_{Q\le1}$) developed PDD within the study period (Figure 2).

The results of the Cox proportional hazard models for both censored and uncensored cohort (excluding dropouts), corrected for covariates, are presented in eTable 6 (links.lww.com/WNL/C307). In the censored cohort (including dropouts), hazard ratios (HR; corrected for between-group covariates) for predicting conversion to PDD were descriptively higher for patients with baseline cognitive IADL impairment (HR = 6.57, 95% CI 2.38–18.17, AIC = 152.00, C-Index = 0.82) than for diagnosis of PD-MCI (HR = 5.34, 95% CI 1.70–16.73, AIC = 161.70, C-Index = 0.80), but highest in patients with both PD-MCI and $FAQ_{Q>1}$ (HR = 12.01, 95% CI 4.47–32.23, AIC = 142.98, C-Index = 0.89, Figure 3).

Change in FAQ Scores Over Time

In all 3 GLMMs calculated for the (uncensored) FAQ total, motor, and cognition scores, the 3-way interaction of time of visit (baseline vs follow-up), baseline cognitive status of PD-CN or PD-MCI, and baseline cognitive IADL status of $FAQ_{Q\le1}$ vs $FAQ_{Q>1}$ was significant ($p \le 0.05$). This indicates that only patients with both PD-MCI and $FAQ_{Q>1}$ showed increase in these FAQ scores between visits (Figure 4 and eTable 7, links.lww.com/WNL/C307). Lower education status (p = 0.048) was associated with higher scores in the FAQ cognition score at both baseline and follow-up visit. Higher scores in the FAQ motor score were related to more severe motor and nonmotor impairment at baseline (MDS-UPDRS-III: p = 0.009; NMSQ: p = 0.041).

Post Hoc ROC Analysis

To verify whether the a priori defined FAQ_Q best defined PDD at the follow-up, a ROC curve analysis evaluating predictive ability of all FAQ subscores was performed. According to the highest Youden Index (J = 0.48, sensitivity = 64.7%, and specificity = 83.7%), a baseline FAQ_Q cut-off value of 1.008 (area under the curve, AUC = 0.72, 95% CI 0.64–0.78, p = 0.0016) was identified to best predict onset of PDD among all scores. The identified cut-off was, therefore, slightly higher than the a priori defined FAQ_Q cut-off >1 used to define cognitive IADL impairment in our sample. Only 2 patients with baseline status of $FAQ_{Q>1}$ in our sample scored below the newly identified FAQ_Q cut-off of 1.008 resulting in a total of 35 (21.3%) patients with values above this defined cut-off. For the FAQ cognition score (AUC = 0.70, 95% CI 0.62–0.77, p = 0.001) and FAQ total score (AUC = 0.67, 95% CI 0.60–0.75, p = 0.005), Youden indices of 0.44 and 0.36, respectively, were identified. The FAQ motor score (AUC = 0.60, 95% CI 0.52–0.67, p = 0.13) was not associated with PDD conversion.

Classification of Evidence

This study provides Class II evidence that impairment of cognitive IADL is associated with progression from PD-MCI to PDD.

Figure 2 Alluvial Plots Detailing Progression of Cognitive Impairment Over Time in Uncensored Data
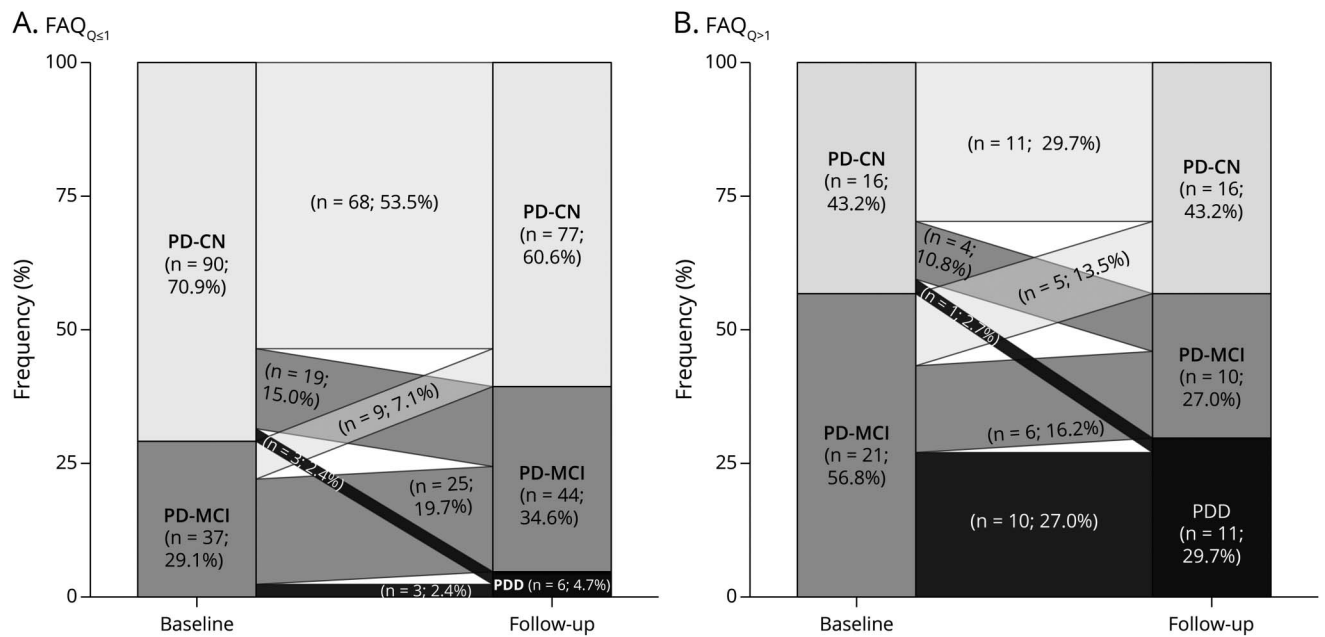
(A) Patients with motor IADL impairment ($FAQ_{Q \leq 1}$). (B) Patients with cognitive IADL impairment ($FAQ_{Q > 1}$). Abbreviations: IADL = instrumental activities of daily living; PD-CN = Parkinson Disease Cognitively Normal; PDD = Parkinson Disease Dementia; PD-MCI = Parkinson Disease with Mild Cognitive Impairment.

Discussion

The current prospective longitudinal cohort study demonstrates that the presence of cognitive IADL impairment, defined using the FAQ_Q cut-off >1, predicts PDD conversion within a short period. The prognostic ability of this defined IADL marker was found to substantially add to the prognostic value of PD-MCI diagnosis, where the combination of cognitive and IADL status best predicted future development of PDD.

In PD, cognition, in addition to other nonmotor aspects, has been confirmed to predict functional decline,[28,29] but knowledge about the predictive ability of cognitive IADL impairment is sparse. Estimated conversion rates from PD-MCI to PDD vary between 20% and 31%, with higher conversion

Figure 3 Survival Curves in Censored Data Showing Predictive Values for PDD Using Different Baseline Stratifications
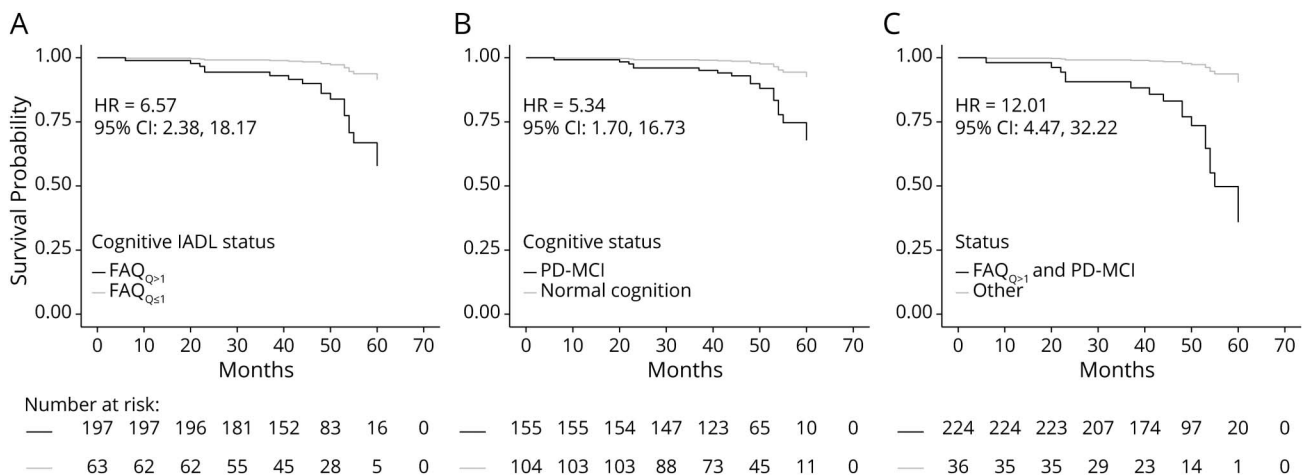
Survival curves were adjusted for covariates and based on multivariate Cox regression models of censored data. (1) Predictive values for PDD in patients stratified by baseline IADL status. (2) Predictive values for PDD in patients stratified by baseline cognitive status. (3) Predictive values for PDD in patients with a combination of cognitive IADL impairment and PD-MCI vs patients with all other statuses. Abbreviations: $FAQ_{Q>1}$ = cognitive IADL impairment; $FAQ_{Q \leq 1}$ = motor IADL impairment; HR = hazard ratio; IADL = instrumental activities of daily living; PDD = Parkinson Disease Dementia; PD-MCI = Parkinson Disease with Mild Cognitive Impairment.

Figure 4 Change in the Functional Activities Questionnaire Total Score Between Uncensored Baseline and Follow-up Data
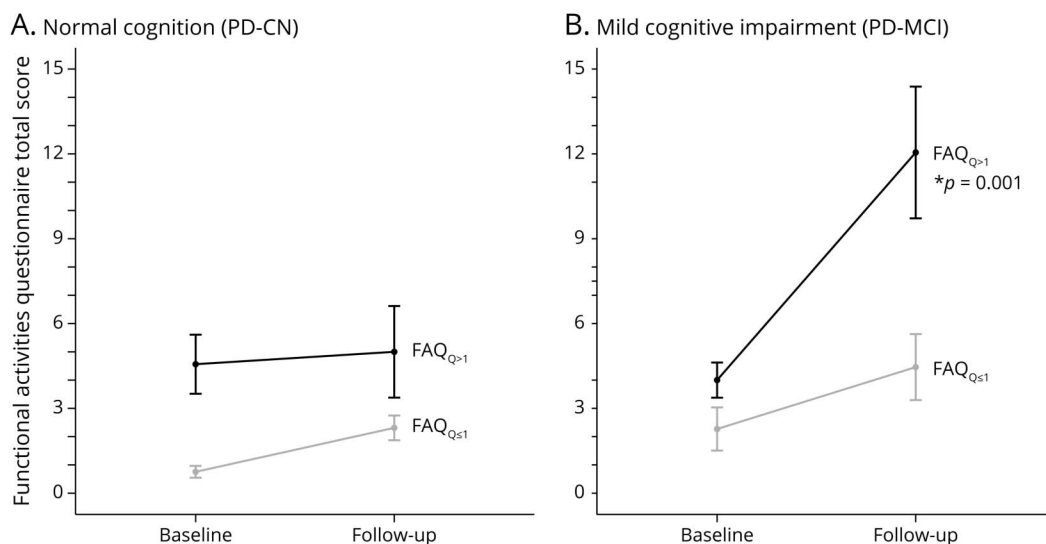
(A) Patients with PD-CN split according to baseline IADL status. (B) Patients with PD-MCI split according to baseline IADL status. Black lines: $FAQ_{Q>1}$ = cognitive IADL impairment, Gray lines $FAQ_{Q\leq1}$ = motor IADL impairment. *Patients classified as both PD-MCI and $FAQ_{Q>1}$ at baseline showed a significant increase between baseline and follow-up visit in the FAQ total scores than patients with baseline status of PD-CN, $FAQ_{Q\leq1}$, or both (3-way interaction, visit*cognitive IADL status*cognitive status, $p = 0.001$). IADL = instrumental activities of daily living; PD-CN = Parkinson Disease Cognitively Normal; PD-MCI = Parkinson Disease with Mild Cognitive Impairment.

rates with a longer follow-up interval.[3] In this study, nearly 50% of patients with PD-MCI and cognitive IADL impairment at baseline converted to PDD, compared with only 8.1% of patients with PD-MCI motor IADL impairment. Because PD-MCI is frequent in PD, the rate of non-PDD converters out of this group is substantial, which negatively affects calculation of risk ratios to define the predictive value. Our data suggest that the combination of PD-MCI and cognitive IADL status can aid in narrowing down patients at high risk for PDD. In addition, only patients with this risk marker profile showed increased progression of IADL function (on all FAQ scores) in our uncensored sample between visits, further strengthening the assumption that IADL function declines in both PDD and its prodromal stage.[6,9,30] This high-risk group might be a valuable target group for clinical trials evaluating the effect of intervention strategies to prevent or delay PDD.

Older age, male sex, and more severe and progressive motor dysfunction have been associated with IADL impairment.[31] In our sample, depressive symptomatology and higher PD-related nonmotor symptoms, but no other demographic or clinical variables, were associated with cognitive IADL impairment. Higher nonmotor burden has previously been reported to be correlated with more severe progression in motor and non–motor-associated function in PD.[30,32] Furthermore, patients with cognitive IADL impairment showed poorer cognitive function in attention, memory, and language domains, reaffirming previously reported results of this baseline cohort and supporting our hypothesis.[16] Previous literature associates worsening of complex performance-based functional impairment with decline in the attention, executive function, memory, and visuospatial abilities domains.[6] In particular, attentional

performance is one of the strongest predictors of everyday function in PDD.[33] Although we also expected a differing profile of CSF biomarkers between patients with cognitive or motor IADL impairment, our current results were not able to show any significant differences in amyloid-beta or tau biomarkers, which need further evaluation in larger PD cohorts. The predictive value of amyloid-beta burden on cognitive worsening and PDD has been verified in previous studies[34,35]; however, the neurobiology underlying IADL function in PD is still unclear. Amyloid-beta burden has been shown to be related to IADL impairment in older age persons with MCI,[36] but to date, studies relating amyloid-beta values to IADL function in PD are lacking. Regarding the genetic risk variants, we did find some differences between patients with cognitive and motor IADL impairment. The role of the *MAPT* gene, which encodes tau, as a risk factor of dementia in PD has been controversially discussed.[37] Because the frequency of the *MAPT* risk H1/H1 genotype was lower in patients with cognitive IADL impairment, who generally showed worse cognitive performance, than patients with motor IADL impairment, our data are in accordance with studies not confirming a link between cognitive function and PD.[38] In addition, we identified a trend for the A-Allele of rs9974126 (which is in high linkage disequilibrium (r2 = 0.93) with rs2248244, a risk factor for PD[39]) in the gene *DYRK1A,* encoding a protein that phosphorylates alpha-synuclein, amyloid-beta precursor protein (APP), and tau.[40]

In PD, differentiation between cognition-driven and motor-driven IADL impairment is difficult because PD-related motor deficits, along with cognitive dysfunction, contribute to IADL impairment.[14,16,41] With sensitive measures, impairments in daily function primarily related to cognitive

dysfunction can be identified in patients with PD without dementia, even in early disease stages.[11,15,41] To date, few measurements have been specifically designed to assess IADL function in PD while being independent of motor impairments.[15,16] In our post hoc ROC analysis, we revealed that the FAQ_Q score best predicted the development of PDD among FAQ subscores, whereas motor-related IADL had no impact on the prediction of PDD conversion. The optimal cut-off identified was slightly higher than the a priori defined FAQ_Q cut-off published previously.[16] Future studies are needed to validate the predictive value of this novel cut-off.

Some limitations of this study need to be mentioned. Although IADL is commonly assessed by an informant who can reliably give information regarding patients' level of functioning, FAQ data were collected from both patients and informants in our study. Although discrepancies between self and informant ratings are greatest in patients with PDD,[42] between-group comparisons on item, total, and subscore levels did not show differences between raters. However, it is known that self-reports on the impact of cognitive changes on IADL function are more sensitive in early stages of cognitive decline.[43] Future studies are needed to evaluate the predictive values of patient vs caregiver ratings in relation to cognitive worsening and dementia. A further limitation is subject attrition, a potential problem for longitudinal studies, and especially so for older patients with PD who are at greater risk of developing other health conditions, institutionalization, and death.[44,45] Approximately 40% of participants did not participate in the follow-up examination, which may have resulted in the loss of valuable information regarding the development of PDD. However, other longitudinal studies examining cognitive decline have reported similar attrition rates: 50% after 5 years[46] and 46% after 4 years[47] Patients in our sample lost to follow-up were older and had more severe motor and cognitive impairments, similar to previous reports.[47] The number of patients with cognitive IADL impairment was not different between patients who dropped out compared with those who were included, suggesting that the presence of cognitive IADL impairment did not affect attrition. There was also a variable length in time to follow-up; however, because the FAQ_Q groups had similar mean intervals, we infer that the time to follow-up did not have a significant effect on our results. Future studies examining predictive value of cognitive IADL impairment should aim for shorter follow-up intervals to minimize attrition and evaluate function at more time points. To minimize selection and nonparticipation bias, we included dropouts in the hazards model classified as PD-CN, the most conservative approach which argues against our hypothesis that baseline IADL status increases the likelihood of PDD. However, we cannot be sure that we identified every patient in the sample who may have developed dementia or that the clinical profile of patients lost to follow-up might have biased our results. Not all patients with PDD were diagnosed according to the Level-II criteria; however, because cognitive testing is not always possible in patients with dementia, detailed medical records were also used for diagnoses. Finally, we cannot rule out that other underlying factors (e.g., vascular burden or cortical atrophy) may have contributed to

faster progression to PDD. There is little research examining how neurobiology or structural brain changes affect IADL function over time. Our data therefore need confirmation in future multicentered studies with a more comprehensive examination including brain imaging to control for underlying neuropathologic effects.

In conclusion, patients with both PD-MCI and cognitive IADL impairment could be a valuable target group for clinical trials evaluating the effect of pharmacologic and nonpharmacological intervention strategies to prevent or delay PDD. Our data argue for the importance of standardized IADL assessment in the prodromal stage of PDD, which is discussed controversially.[48] Especially in early stages of cognitive impairment, systematic assessment of everyday function might be neglected by physicians in the clinical daily routine. We propose a two-step screening approach: First, the application of a standardized IADL scale to screen for patients with cognitive IADL impairment, and second, the evaluation of the impact of these problems in a patient-centered interview for diagnostic purposes.

Disclosure
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Publication History

Appendix Authors

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Merle Bode, BSc	University of Tübingen, Tübingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data

Appendix *(continued)*

Name	Location	Contribution
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Katja Michaelis	University of Tübingen, Tübingen, Germany	Major role in the acquisition of data
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Walter Maetzler, MD	Christian-Albrechts-University, Kiel, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
Milan Zimmermann, MD	University of Tübingen, Tübingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
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Inga Liepelt-Scarfone, PhD	University of Tübingen, Tübingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

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