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Abstract

Background: Health-related quality of life (HrQoL) is impacted in Parkinson's disease (PD) and has also been reported to be affected in idiopathic REM-Sleep Behaviour Disorder. This study aims to understand whether HrQoL is associated with risk factors and prodromal features of PD in a population-based cohort.

Methods: Data were obtained from two longitudinal population-based studies: HeBA and PREDICT-PD. Participants provided demographic information and reported key subjective prodromal symptoms. They also completed the European HrQoL Questionnaire (EQ-5D-5L) including the Visual Analogue Scale (EQ-VAS). Depending on the cohort, assessments included the Non-Motor Symptom Questionnaire (NMSQ), the Movement Disorder Society-Unified PD Rating Scale (MDS-UPDRS) Ib and II, and the Penn Daily Activity Questionnaire for PD (PDAQ). Olfaction was remotely assessed with the University of Pennsylvania Smell Identification Test (UPSIT). MDS probabilities for prodromal PD and/or the PREDICT-PD risk score were calculated.

Results: From HeBA 3207 participants (57.3% female) were included, with a median age of 60 years (IQR: 55.0–66.0) and 15 (12.0–18.0) years of education. From PREDICT-PD 1528 participants (60.7% female) were included, with a median age of 69.5 (66.5–73.7) years and 17 (14.0–20.0) years of education. The median EQ-5D-5L Index was 0.94 (0.89–1.0) in HeBA and 0.96 (0.90–1.0) in PREDICT-PD, with a median EQ-VAS score of 85 (75–90) across both cohorts. In HeBA, lower HrQoL was associated with higher NMSQ, MDS-UPDRS Ib and II scores, and lower PDAQ scores [all $p<0.001$; adjusted for sex, age, centre, Charlson Comorbidity Index (CCI), Body Mass Index (BMI), education years, and living alone]. In PREDICT-PD, reduced HrQoL was associated with higher MDS-UPDRS Ib and II scores (both $p<0.001$; adjusted for sex, age, CCI, BMI, and education years). Finally, lower HrQoL was associated with higher MDS probabilities for prodromal PD (in both HeBA and PREDICT-PD, $p<0.001$) and higher frequency of reported subjective symptoms.

Conclusion: Our findings suggest that lower HrQoL scores are associated with increased scores for motor and non-motor symptoms and cognitive complaints in healthy individuals. Ongoing longitudinal follow-up assessments will facilitate further understanding of HrQoL trajectories with progression to early disease stages.

INTRODUCTION

Health-related quality of life (HrQoL) is significantly compromised in people with Parkinson's disease (PD) (Soh et al., 2011), a neurodegenerative disorder characterized by motor disturbances such as rigidity, bradykinesia, and impaired gait with freezing. In addition to these motor symptoms, patients often experience a range of non-motor symptoms, including mild cognitive impairment, mood disturbances, sleep problems, and, in advanced stages, dementia and psychosis (Poewe et al., 2017). These symptoms can notably impact the patients' HrQoL, particularly affecting the physical and psychological subdomains (Prasuhn et al., 2017; Zhao et al., 2021), both of which are known to also be associated with the presence of non-motor symptoms (Röttgen et al., 2025). HrQoL has also been increasingly used as an outcome measure in clinical trials in PD (Martinez-Martin & Kurtis, 2012; Schuepbach et al., 2013).

Before PD is clinically diagnosed, different non-motor symptoms such as idiopathic REM Sleep Behaviour Disorder (iRBD), hyposmia, anxiety or depression can be present (Heinzel et al., 2019; Poewe et al., 2017) and may also affect HrQoL. While there is already evidence that iRBD negatively affects HrQoL (Dauvilliers et al., 2018; Röttgen et al., 2025), less is known about its relationship with other early risk factors and prodromal features.

This study used the European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L) instrument measured in two large population-based studies on PD-risk identification, the Healthy Brain Ageing (HeBA) multicentre cohort, and the UK PREDICT-PD cohort. We aimed to assess whether current HrQoL is associated with various PD risk factors and overall risk for PD as determined by calculating the probability of prodromal PD.

METHODS

1. Healthy Brain Aging (HeBA) Study and PREDICT-PD Study

The HeBA Study is a prospective European multicentre study [Medical University of Innsbruck (MUI) in Austria, National Centre of Excellence in Research on PD in Luxembourg (NCER-PD), Hospital Clinic Barcelona (HCB) in Spain, and the Paracelsus-Elena-Klinik Kassel (PEKK) in Germany] aimed at identifying risk factors for the development of PD and/or dementia associated syndromes in the general population (Schade et al., 2025). It uses an initial internet-based approach to recruit persons from the general population, aged 50 years and above, for an online evaluation of baseline characteristics and risk factors for PD, followed by remote smell testing (University of Pennsylvania Smell Identification Tests; UPSIT (Doty et al., 1984)). The inclusion criteria comprised residency within the countries of the HeBA centres, aged ≥50 years, and the absence of pre-existing PD, dementia, or other clinically significant central nervous system disorders associated with anticipated neurological deficits. Subsequently, some participants are invited to in-person visits for a more thorough assessment of risk and prodromal markers. The study began in 2022 and is ongoing, with a recruitment of close to 30,000 people across the four centres (Schade et al., 2025).

The PREDICT-PD Study is a UK-based prospective study focusing on identifying people (aged ≥ 50 years) at high risk of developing PD before symptoms appear. The study started in 2011 and is ongoing, with more than 13,000 participants. Participants complete various online questionnaires, computer tests and remote assessments related to PD risk factors, aiming to identify those at increased risk. The inclusion criteria (Noyce et al., 2014) is being a resident of the UK, aged 50–80 years, without pre-

existing PD or other specific neurological conditions, and not using drugs associated with Parkinsonism. Participants complete annual online surveys and tests as well as remote smell tests and biosample collection. Subsequently, some sub-cohorts are invited for in-person visits to undergo detailed phenotyping, as outlined in detail elsewhere (Virameteekul et al., 2026).

2. Study participants

For the present study, data from HeBA was used from the Innsbruck and Luxembourg sites, as these were the only two centres that implemented the full EQ-5D-5L. We extracted data from the remote study cohort acquired between April 2022 and January 2025 from participants with a complete online assessment and smell test data available (Innsbruck n = 1523; Luxembourg n = 1730). Participants with a diagnosis of interest at baseline were excluded (n=8; 6 PD, 1 dementia and 1 amyotrophic lateral sclerosis). In addition, 38 participants were excluded due to not having completed the EQ-5D-5L. The final number of participants for the present analysis was 3207 participants (Supplementary Figure 1).

For PREDICT-PD, data were extracted from the remote study cohort at sessions 5 and 6, which took place between 2019 and 2023. The EQ-5D-5L data was collected only at session 5, while some other information of interest was obtained at session 6 (with less than one year gap between sessions 5 and 6). Of the 3887 participants who answered the EQ-5D-5L at session 5, only those with complete EQ-5D-5L assessment were included, resulting in a final sample of 1528 participants.

3. Participant Assessment

During the online assessment, the following information was collected (Supplementary Table 1 shows the different assessment tools/questions used for each cohort):

1. Demographics (sex, age, and education years), Body Mass Index (BMI) and medical history (medical conditions based on Charlson Comorbidity Index (CCI); (Charlson et al., 1987; Schade et al., 2025)) as well as five single high-interest questions (HIQ) with a "yes/no" answer on family history of PD, subjective dream enactment behaviour (modified from the RBD Single-Question Screen (Postuma et al., 2012), subjective hyposmia (both cohorts), family history of AD, and subjective memory impairment (HeBA only).
   The HIQ regarding subjective smell capacity in the HeBA cohort was a dichotomous question ("Do you have problems with your sense of smell?"), whereas for PREDICT-PD, it was a self-rated sense of smell on a scale from 0 to 10.
2. Non-motor symptoms questionnaires:
   - **Non-Motor Symptom Questionnaire (NMSQ)**: a 30-item scale in which participants have to indicate with "yes" or "no" the presence of non-motor symptoms (i.e., constipation, feeling sad or feeling dizzy) in the last month (Chaudhuri et al., 2005). For the present analysis, the items related to pain/discomfort (number 10 and 26) and anxiety/depression (number 16 and 17) were removed from the NMSQ score ($NMSQ^{m}$) to avoid overlap with these two domains from the EQ-5D-5L.
   - **Movement Disorder Society – Unified Parkinson's disease Rating Scale part Ib (MDS-UPDRS Ib)**: MDS-UPDRS I is a 13-item test that evaluates the non-motor aspects of daily living using a 5-point Likert scale (from "0-normal" to "4-severe"). Participants have to indicate their average level of functioning in activities of daily living, such as urinary problems, constipation or

daytime sleepiness (Goetz et al., 2008). Due to the remote nature of the study, only the items that allow self-assessment (i.e. items 7 to 13 = part Ib) were included. For the present analysis, the item on pain/discomfort (number 9) was removed from the MDS-UPDRS Ib total score to avoid overlap (MDS-UPDRS Ib^m), as pain is also a domain of the EQ-5D-5L.

- **Penn Parkinson's Daily Activities Questionnaire-15 (PDAQ):** a 15-item questionnaire where participants have to rate on a 5-point Likert scale from to "0-cannot do" to "4-none" their abilities to do instrumental cognitive activities of daily living (i.e., having difficulties when doing more than one thing at the same time or during a discussion about a TV show or book). The higher the score, the better the performance (Brennan et al., 2016). For the present analysis, the items related to the ability to perform usual activities (number 1, 3, 11, 12, 13, and 14) were removed from the PDAQ score ($PDAQ^m$) to avoid overlap with the "usual activities" domain of the EQ-5D-5L.

3. Motor symptoms questionnaires:
   - **Movement Disorder Society – Unified Parkinson's Disease Rating Scale part II (MDS-UPDRS II)**: this is a 13-item test with a 5-point Likert scale (from "0-normal" to "4-severe") that measures motor experiences of daily living, such as difficulties getting out of the bed or problems walking or maintaining balance (Goetz et al., 2008). For the present analysis, the items related to mobility (number 11, 12 and 13), self-care (number 5 and 6), and usual activities (number 8), were removed from the MDS-UPDRS II (MDS-UPDRS II^m) total score to avoid overlap with the EQ-5D-5L.

4. HrQoL:
   - **European Quality of Life 5-Dimension 5-Level (EQ-5D-5L)**: it measures five health dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) using five levels of severity (no problems, slight problems, moderate problems, severe problems, and unable to do it) (Brooks, 1996; Herdman et al., 2011). Based on the response to these five dimensions of health, EQ-5D-5L indices were calculated using a published algorithm and response data co-administered in six European countries (Denmark, England, Italy, the Netherlands, Poland, and Scotland) (Van Hout et al., 2012), which represents the participant's health status, the EQ-5D-5L Index, with values from <0 to 1 (negative values represent a health status worse than dead; 0 represents a health status equivalent to dead; 1 represents the best health status) (Devlin et al., 2022). Following the population norms published by the EuroQol website (https://euroqol.org/), since there are no available value sets for Austria and Luxembourg, we used the German value set (Ludwig et al., 2018) for the HeBA cohort and the United Kingdom value set (Rowen et al., 2026) for the PREDICT-PD cohort.
   - **EuroQol Visual Analogue Scale (EQ-VAS)**: participants have to indicate how good their overall health is "today" on a 0 ("worst health you can imagine") to 100 ("best health you can imagine") points scale (Devlin et al., 2020).

5. Smell test:
   - The full **University of Pennsylvania Smell Identification Test (UPSIT)** with 40 scratch-and-sniff items was used in the HeBA study. The person has to smell each odour and indicate which of four odour options is the correct one. This test was sent to all participants by post for completion at home and online return of results. Age- and sex-adjusted UPSIT percentiles were calculated according to established cut-offs (Brumm et al., 2023). Consistent with the Parkinson At-Risk Syndrome Study (PARS), when the UPSIT percentile was at or below the 15^{th} percentile, hyposmia (a reduced sense of smell) was defined (Siderowf et al., 2012).

- The PREDICT-PD smell test used in the present study was assessed by a brief version of the UPSIT comprising six odours (Bestwick, Auger, Schrag, et al., 2021). This test was also sent to the participants by post for completion at home, and they input their answers on a corresponding questionnaire on the PREDICT-PD website.

6. Risk estimation approaches:
   - **Movement Disorders Society – probabilities of prodromal PD (MDSppPD)**: According to the updated MDS research criteria for prodromal PD (Berg et al., 2015; Heinzel et al., 2019) probabilities of prodromal PD were calculated. This algorithm considers age as a pre-test probability, depending on age and items related to the likelihood of developing PD in the future. These factors are integrated into post-test probabilities, ranging from 0% to 100% for lowest to highest probabilities. The variables available and included to calculate the MDSppPD were: sex, regular pesticide exposure, occupational solvent exposure, non-use of caffeine, smoking condition (current, never or former), first-degree family member with PD, *Diabetes mellitus* type II, and physical inactivity as risk factors; and dream enactment behaviour, constipation, excessive daytime somnolence, orthostatic hypotension, erectile dysfunction, urinary dysfunction, and instrumental cognitive activities (measured with the PDAQ) as prodromal factors. The variables that were left out to avoid overlap were depression and anxiety, as these constructs are domains in the EQ-5D-5L. Additionally, we calculated the MDSppPD including olfactory dysfunction (≤15th percentile according to (Brumm et al., 2023)) from the UPSIT test results (MDSppPD≤15th). Factors with high likelihoods such as dopaminergic imaging were not available due to the population-based design.
   - **PREDICT-PD Risk Score (PREDICT-PD r.s.)** (Bestwick, Auger, Simonet, et al., 2021; Noyce et al., 2014): the PREDICT-PD study developed its own algorithm to provide PD risk scores. The variables included were age, gender, smoking status, family history of PD, coffee use, alcohol use, hypertension, non-steroidal anti-inflammatory drug use, calcium channel blocker use, β blocker use, constipation, previous head injury, and erectile dysfunction (only in men). The variables that were not included to avoid overlap (as they are part of the EQ-5D-5L) were depression and anxiety. The PREDICT-PD r.s. (presented as an odds) was inversely related to estimated PD risk; that is, lower scores indicated higher estimated risk. The score is expressed as odds of 1 in X, e.g. the 1 in 2 indicates substantially higher risk than the 1 in 1000.

4. Statistical analysis

Analogous analyses were conducted independently for the HeBA and PREDICT-PD datasets.

Descriptive statistics were used to describe demographic, personal, and clinical characteristics including median, interquartile range (IQR), frequencies, and percentages. Non-parametric statistical methods were employed as data were mostly not normally distributed. The significant *p*-value was ≤0.05.

To explore the relationship between high-risk factors and HrQoL, Spearman-rank correlation analysis was used to calculate correlation coefficients between EQ-5D-5L Index, EQ-VAS and different variables (e.g. HIQs, NMSQ^{m}, MDS-UPDRS Ib^{m}, MDS-UPDRS II^{m}, PDAQ^{m}, UPSIT raw score, UPSIT percentile, MDSppPD, PREDICT-PD r.s.; Supplementary Tables 2 and 3). Variables showing statistical significance were further included in linear regression models that adjust for factors known to influence

HrQoL. In both cohorts, three different models were run: Model 1) unadjusted; Model 2) adjusted for age and sex, as well as study centre (i.e. the Innsbruck or Luxembourg sample) in the HeBA cohort; and Model 3) adjusted for sex, age, CCI, BMI, and years of education (plus centre and living alone in the HeBA cohort). For this analysis EQ-5D-5L indices were rescaled by multiplying individual values by 100 in order to render resulting regression coefficients (B) better interpretable; in this rescale 1 point corresponds to 0.01 units on the original EQ-5D-5L scale, for example 94 index points correspond to 0.94 units on the original EQ-5D-5L scale.

Furthermore, to gain a deeper understanding of how the MDSppPD may be specific to each of the HrQoL dimensions, we performed different ordinal logistic regression analyses with each dimension of the EQ-5D-5L (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as the dependent variable.

All statistical analyses were performed using IBM SPSS Statistics Version 29.0.

RESULTS

1. Population characteristics and clinical information

Detailed clinical data and HIQ information collected via online assessment from the HeBA and PREDICT-PD participants are summarized in Table 1. From the total HeBA sample (descriptive characteristics of each centre can be found in Supplementary Table 4), 1838 (57.3%) were female, the median age was 60 (IQR: 55 - 66), the median education years was 15 (12 - 18), and the median CCI was 0 (0 - 0). From the total 1528 PREDICT-PD participants, 927 (60.7%) were female, the median age was 69.5 (66.5 - 73.7), the median education years was 17 (14 - 20), and the median CCI was 3 (2 - 3).

In the HEBA and PREDICT-PD cohorts, the median scores for the EQ-5D-5L Index were 0.94 (IQR: 0.89 - 1.00) and 0.96 (0.90 – 1.00), respectively, and the median EQ-VAS (Figure 1) score was 85 (75 - 90) in both. The number of motor and non-motor symptoms was low in both cohorts. Participants from the HeBA cohort had a higher median MDSppPD≤15th (median: 1.2, IQR: 0.4 – 4.2) compared to PREDICT-PD participants (median: 0.5, IQR: 0.3 – 2.7).

Table 1. Demographic and clinical information from the HeBA and PREDICT-PD cohorts.

Variable	HeBA	PREDICT-PD
n Total	3207	1528
n Female	1838 (57.3%)	927 (60.7%)
Age	60 (55.0 – 66.0)	69.5 (66.5 - 73.7)
Education years	15 (12.0 - 18.0)	17 (14.0 - 20.0)
Education levels		
No school	n.a.	18 (1.2%)
Primary School	139 (4.3%)	7 (0.5%)
Secondary School	789 (24.7%)	123 (8.0%)
Further/A-level	880 (27.5%)	365 (23.9%)

Higher education	1388 (43.4%)	1015 (66.4%)
Not answered	11 (0.3%)	0 (0%)
Occupational status		
Specialist highly educated	1120 (34.9%)	1464 (95.9%)
Skilled labour	790 (24.7%)	36 (2.4%)
Unskilled labour	45 (1.4%)	15 (1.0%)
Other	n.a.	11 (0.7%)
Not answered	1252 (39%)	2 (0.1%)
Employment status		
Employed	1730 (54.0%)	189 (12.4%)
Unemployed	56 (1.7%)	11 (0.7%)
Retired	1398 (43.6%)	1326 (86.8%)
Not answered	23 (0.7%)	2 (0.1%)
Living arrangement		
Living alone	659 (20.5%)	n.a.
Living with partner	2238 (69.8%)	n.a.
Living in house with caregiver facilities	4 (0.1%)	n.a.
Living in nursing home	2 (0.1%)	n.a.
Not answered	12 (0.4%)	n.a.
Regular physical activity	2240 (69.8%)	556 (36.4%)
CCI (nº of comorbidities)	0 (0.0 - 0.0)	3 (2.0 - 3.0)
0 1 2 3 >3 Not answered	2424 (75.6%) 537 (16.7%) 167 (5.2%) 46 (1.4%) 33 (1.1%) n.a.	n.a. 15 (1%) 556 (36.6%) 571 (37.6%) 376 (24.1%) 10 (0.7%)
BMI	25.1 (22.7- 28.4)	24.6 (22.3 – 27.8)
HIQ 1st degree PD	451 (14.1%)	336 (22.0%)
HIQ 1st degree AD	413 (12.8%)	n.a.
HIQ Subjective Dream Enactment Behavior	1261 (39.3%)	951 (62.2%)
HIQ Subjective Memory Impairment	613 (19.1%)	n.a.
HIQ Subjective Hyposmia (yes/no)	545 (17.0%)	n.a.
Self-rated sense of smell from 0 to 10 scale Session 6	n.a.	10 (9.0 - 10.0)

0 1 - 3 4 - 6 7 - 10 Not answered	n.a.	43 (2.8%) 75 (4.9%) 84 (5.5%) 1324 (86.7%) 2 (0.1%)
EQ-5D-5L Index	0.94 (0.89 - 1.0)	0.96 (0.90 – 1.0)
EQ-VAS	85 (75 - 90)	85 (75 - 90)
NMSQ	5 (2 - 8)	n.a.
NMSQ^{m}	4 (2 - 7)	n.a.
MDS-UPDRS Ib	4 (2.0 - 6.0)	4.7 (2 - 7)
MDS-UPDRS Ib^{m}	3.0 (2 - 6)	3.6 (1.2 – 6.0)
MDS-UPDRS II	0 (0 - 2)	0 (0 - 2)
MDS-UPDRS II^{m}	0 (0 - 1)	0 (0 - 1)
PDAQ	57 (54 - 59)	n.a.
PDAQ^{m}	34 (32 - 35)	n.a.
MDSppPD	1.1% (0.4 – 3.0)	n.a.
UPSIT 40-Items	31 (28 - 34)	n.a.
UPSIT 6-Items	n.a.	4 (4 - 5)
n UPSIT smell test score ≤15th percentile	1121 (35.0%)	242 (15.9%)
MDSppPD≤15th	1.2% (0.4 – 4.2)	0.5% (0.3 – 2.7)
Median PREDICT-PD r.s.	n.a.	1 : 33.9 (1 : 16.1 – 1 : 55.7)

Values are expressed as median (25th - 75th percentile) or frequencies (percentage), according to the type of variable. ^{m} "mobility", "self-care", "usual activities", "pain/discomfort", and/or "anxiety/ depression" related items were not included as these overlap with the EQ-5D-5L. AD, Alzheimer's disease; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; HIQ, high-interest questions; EQ-5D-5L, European Quality of Life 5-Dimensions 5-Levels; EQ-VAS, European Quality of Life - Visual Analogue Scale; MDS-UPDRS, Movement Disorders Society - Unified Parkinson´s Disease Rating Scale; MDSppPD, Movement Disorders Society probabilities for prodromal PD; MDSppPD≤15th, Movement Disorders Society probabilities for prodromal PD with UPSIT ≤15 percentile; NMSQ, Non-Motor Symptoms Questionnaire; PD, Parkinson's disease; PDAQ, Penn Parkinson's Daily Activities Questionnaire-15; r.s., risk score; UPSIT, University of Pennsylvania Smell Identification Tests.

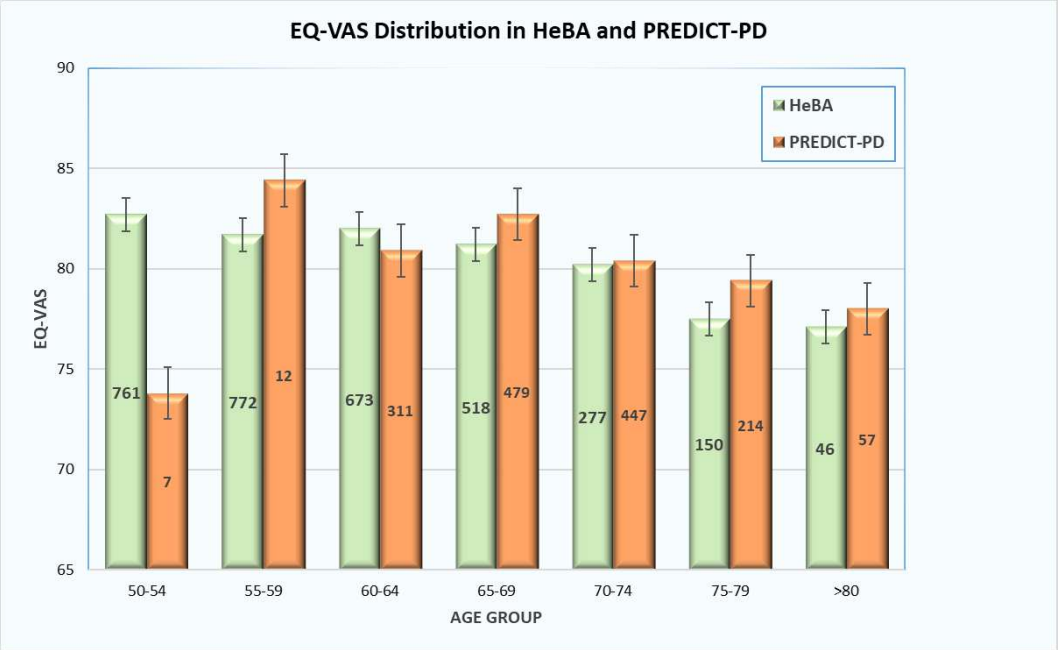


Figure 1. EQ-VAS distribution in HeBA and PREDICT-PD cohort by age-group. The number of participants are present in the middle of the bar.

2. HrQoL

In both cohorts (Table 2; information about HeBA sites can be found in Supplementary Table 5), the most frequently reported level was "no problems," except in the "pain/discomfort" dimension within the HeBA cohort, where "slight problems" was more commonly reported. Severe problems in any dimension were rare, with "pain/discomfort" being the most impaired dimension in the HeBA cohort and "anxiety/depression" in the PREDICT-PD cohort.

Table 2: EQ-5D-5L frequencies (percentages) reported by dimension and level.

		MOBILITY n (%)	SELF-CARE n (%)	USUAL ACTIVITIES n (%)	PAIN / DISCOMFORT n (%)	ANXIETY / DEPRESSION n (%)
Level 1 (No problems)	**HeBA**	2531 (78.9%)	3119 (97.3%)	2737 (85.3%)	1122 (35.0%)	1999 (62.3%)
	PREDICT-PD	1330 (87.0%)	1490 (97.5%)	1358 (88.9%)	828 (54.2%)	1065 (69.7%)
Level 2 (Slight problems)	**HeBA**	475 (14.8%)	66 (2.1%)	346 (10.8%)	1451 (45.2%)	917 (28.6%)
	PREDICT-PD	147 (9.6%)	31 (2.0%)	140 (9.2%)	555 (36.3%)	380 (24.9%)
Level 3 (Moderate problems)	**HeBA**	147 (4.6%)	16 (0.5%)	90 (2.8%)	538 (16.8%)	246 (7.7%)
	PREDICT-PD	41 (2.7%)	7 (0.5%)	23 (1.5%)	133 (8.7%)	70 (4.6%)
Level 4 (Severe problems)	**HeBA**	49 (1.5%)	4 (0.1%)	30 (0.9%)	84 (2.6%)	38 (1.2%)
	PREDICT-PD	10 (0.7%)	n.a.	6 (0.4%)	10 (0.7%)	10 (0.7%)
Level 5 (Extreme problems)	**HeBA**	5 (0.2%)	2 (0.1%)	4 (0.1%)	12 (0.4%)	7 (0.2%)
	PREDICT-PD	n.a.	n.a.	1 (0.1%)	2 (0.1%)	3 (0.2%)

3. Factors associated with HrQoL scores

The correlation results (Supplementary Tables 2 and 3) showed that lower HrQoL correlated with greater subjective symptoms experience (HIQs), higher number of motor and non-motor symptoms, higher MDSppPD, and lower PREDICT-PD r.s., corresponding to higher estimated PD risk (i.e. lower odds of PD in the PREDICT-PD r.s.).

Two linear regression analyses were performed for both cohorts to predict EQ-5D-5L Index and EQ-VAS score (as dependent variables), for which EQ-5D-5L Index were rescaled by multiplying individual values by 100 in order to render resulting regression coefficients (B) better interpretable (see methods for example). In the HeBA cohort (Table 3), in Model 1, all variables were significantly associated with EQ-5D-5L Index. A lower EQ-5D-5L Index was associated with being female, being older, being from the Luxembourg centre, having fewer years of education, living alone, higher CCI and BMI scores, reporting positive answers to the HIQs, higher motor and non-motor symptoms, and higher MDSppPD. In Model 2, the previously significant variables remained significant, and in Model 3, experiencing subjective hyposmia no longer reached significance (β=-1.05, p=0.061).

Table 3. Results from the HeBA cohort linear regression with EQ-5D-5L Index as the dependent variable.

	Model 1: Unadjusted		**Model 2: Adjusted for sex, age and centre**		**Model 3: Adjusted for sex, age, centre, CCI, BMI, education years, and living alone**	
	B, *p*	**R^2 Corr.**	**B, *p***	**R^2 Corr.**	**B, *p***	**R^2 Corr.**
Sex	-1.23, 0.006	0.002	-	-	-	-
Age	-0.08, 0.006	0.002	-	-	-	-
Centre	**3.03, <0.001**	0.014	-	-	-	-
Education years	**0.27, <0.001**	0.010	**0.25, <0.001**	0.029	-	-
Living alone	**-2.51, <0.001**	0.006	**-2.13, <0.001**	0.027	-	-
CCI	**-4.77, <0.001**	0.094	**-4.82, <0.001**	0.114	-	-
BMI	**-0.49, <0.001**	0.037	**-0.50, <0.001**	0.060	-	-
HIQ Subjective Dream Enactment Behavior	**-4.00, <0.001**	0.024	**-3.30, <0.001**	0.036	**-2.34, <0.001**	0.144
HIQ Subjective Memory Impairment	**-7.36, <0.001**	0.053	**-7.21, <0.001**	0.072	**-5.85, <0.001**	0.171
HIQ Subjective Hyposmia	**-2.20, <0.001**	0.004	-1.39, 0.019	0.024	-1.05, 0.061	0.138
NMSQ Sum^m	**-1.75, <0.001**	0.259	**-1.71, <0.001**	0.262	**-1.45, <0.001**	0.300
MDS-UPDRS Ib^m	**-2.22, <0.001**	0.270	**-2.20, <0.001**	0.278	**-1.88, <0.001**	0.316
MDS-UPDRS II^m	**-3.17, <0.001**	0.196	**-3.20, <0.001**	0.216	**-2.61, <0.001**	0.259
PDAQ^m	**1.14, <0.001**	0.139	**1.10, <0.001**	0.150	**0.96, <0.001**	0.230
MDSppPD*	**-0.72, <0.001**	0.171	**-0.70, <0.001**	0.176	**-0.55, <0.001**	0.216
MDSppPD≤15th*	**-0.39, <0.001**	0.121	**-0.28, <0.001**	0.129	**-0.29, <0.001**	0.194

[m] "mobility", "self-care", "usual activities", "pain/discomfort", and/or "anxiety/ depression" related items were not included as these constructs overlap with the content of EQ-5D-5L. *Sex and age are already included in the MDSppPD and were therefore not included in the present linear regression analyses.
P-Values in bold are below the Bonferroni-adjusted level of significance of 0.001.
BMI, Body Mass Index; CCI, Charlson Comorbidity Index; HIQ, high-interest questions; MDSppPD, Movement Disorders Society probabilities for prodromal PD; MDSppPD≤15th, Movement Disorders Society probabilities for prodromal PD with UPSIT ≤15 percentile; MDS-UPDRS, Movement Disorders Society - Unified Parkinson´s Disease Rating Scale; NMSQ, Non-Motor Symptoms Questionnaire; PDAQ, Penn Parkinson's Daily Activities Questionnaire-15; UPSIT, University of Pennsylvania Smell Identification Test.

In the PREDICT-PD cohort (Table 4), Model 1 showed that higher CCI and BMI scores, experiencing subjective dream enactment behavior and poorer self-rated sense of smell, higher motor and non-motor symptoms, and higher probabilities for prodromal PD were associated with a lower EQ-5D-5L Index. In Model 2 and Model 3, the previously significant variables remained significant.

Table 4. Results from the PREDICT-PD cohort from the linear regression with EQ-5D-5L Index as the dependent variable.

	Model 1: Unadjusted		**Model 2: Adjusted for sex and age**		**Model 3: Adjusted for sex, age, CCI, BMI, and education years**	
	B, *p*	**R^2 Corr.**	**B, *p***	**R^2 Corr.**	**B, *p***	**R^2 Corr.**
Age	-0.48, 0.276	0.000				
CCI	**-0.83, <0.001**	0.012	**-1.05, <0.001**	0.014	-	-
BMI	**-0.42, <0.001**	0.049	**-0.43, <0.001**	0.051	-	-
HIQ Subjective Dream Enactment Behavior	-1.46, 0.004	0.005	-1.48, 0.003	0.006	-1.31, 0.009	0.065
Self-rated sense of smell	**0.32, 0.001**	0.006	**0.32, 0.001**	0.007	**0.33, <0.001**	0.068
MDS-UPDRS Ib[m]	**-1.34, <0.001**	0.240	**-1.36, <0.001**	0.243	**-1.28, <0.001**	0.267
MDS-UPDRS II [m]	**-2.55, <0.001**	0.145	**-2.59, <0.001**	0.148	**-2.40, <0.001**	0.185
PREDICT-PD r.s.*	**0.03, <0.001**	0.012	**0.03 <0.001**	0.013	**0.03, 0.002**	0.068
MDSppPD≤15th*	**-0.10, <0.001**	0.014	**-0.10, <0.001**	0.014	**-0.08, <0.001**	0.068

The variables with [m] mean that "mobility", "self-care", "usual activities", "pain/discomfort", and/or "anxiety/ depression" related items were not included as these represent domains in the EQ-5D-5L. *Sex and/or age are already included in the MDSppPD and PREDICT-PD r.s. and were therefore not included in the present linear regression analyses.
P-Values in bold are below the Bonferroni-adjusted level of significance of 0.002. BMI, Body Mass Index; CCI, Charlson Comorbidity Index; HIQ, high-interest questions; MDS-UPDRS, Movement Disorders Society - Unified Parkinson´s Disease Rating Scale; MDSppPD≤15th, Movement Disorders Society probabilities for prodromal PD with UPSIT ≤15 percentile; r.s., risk score; UPSIT, University of Pennsylvania Smell Identification Test.

In addition, we ran a second linear regression analysis to identify which factors of the ones used in the previous linear regression analysis would also be associated with the EQ-VAS.

In the HeBA cohort (Supplementary Table 6), Model 1 showed that lower EQ-VAS scores were associated with older age, recruitment at the Luxembourg study centre, higher CCI and BMI scores, fewer years of education, living alone, subjective symptoms in each of the three HIQ domains, more

severe motor and non-motor symptoms, lower UPSIT scores, and a higher MDSppPD. In Model 2, all variables that were significant in Model 1 remained significant, except for UPSIT score. In Model 3, neither UPSIT score nor subjective hyposmia reached statistical significance.

In the PREDICT-PD cohort (Supplementary Table 7), Model 1 shows that lower scores in EQ-VAS were associated with being older, higher CCI and BMI scores, lower education years, experiencing subjective symptoms, such as dream enactment behaviour, higher motor and non-motor symptoms, and higher probabilities to develop PD. In Model 2, years of education were no longer significantly associated with EQ-VAS. In Model 3, the MDSppPD was no longer associated with EQ-VAS.

4. Prediction of HrQoL domains by probability for prodromal PD and PREDICT-PD

An ordinal logistic regression analysis (Table 5) was run to understand which EQ-5D-5L domains were influenced by changes in the MDSppPD≤15th. In the HeBA cohort we found that higher MDSppPD were associated with higher, i.e. worse scores in all EQ-5D-5L domains (all adjusted for centre, CCI, BMI, education years, and living alone;).

In the PREDICT-PD cohort, we did not find a significant association between MDSppPD and EQ-5D-5L subdomains. Regarding the PREDICT-PD r.s., higher risk of PD as indicated by lower PREDICT-PD r.s. was associated with higher impairment in mobility, usual activities, pain/discomfort, and depression/anxiety (all adjusted for CCI, BMI, and education years).

Table 5. Ordinal logistic regression for **EQ-5D-5L** domains in the HeBA and PREDICT-PD cohorts.

	VI	B	*SD*	*p*	Odds Ratio	Lower 95%CI	Upper 95%CI	R^2
Mobility								
HeBA	MDSppPD≤15th	0.028	0.003	<0.001	1.029	1.022	1.036	0.195
PREDICT-PD	MDSppPD≤15th	0.011	0.006	0.059	1.011	1.000	1.023	0.126
	PREDICT-PD r.s.	-0.011	0.003	<0.001	0.989	0.983	0.995	0.153
Self-care								
HeBA	MDSppPD≤15th	0.039	0.005	<0.001	1.040	1.030	1.051	0.170
PREDICT-PD	MDSppPD≤15th	0.014	0.009	0.128	1.014	0.996	1.033	0.086
	PREDICT-PD r.s.	-0.009	0.009	0.304	0.991	0.975	1.008	0.104
Usual activities								
HeBA	MDSppPD≤15th	0.034	0.004	<0.001	1.035	1.027	1.042	0.167
PREDICT-PD	MDSppPD≤15th	0.011	0.006	0.055	1.011	1.000	1.023	0.083
	PREDICT-PD r.s.	-0.010	0.004	0.010	0.990	0.982	0.998	0.098
Pain/Discomfort								
HeBA	MDSppPD≤15th	0.028	0.003	<0.001	1.029	1.022	1.035	0.124
PREDICT-PD	MDSppPD≤15th	0.006	0.005	0.223	1.006	0.997	1.015	0.070
	PREDICT-PD r.s.	-0.009	0.002	<0.001	0.991	0.987	0.995	0.095
Anxiety/Depressin								
HeBA	MDSppPD≤15th	0.030	0.003	<0.001	1.030	1.023	1.037	0.090
PREDICT-PD	MDSppPD≤15th	0.005	0.005	0.306	1.005	0.995	1.015	0.004
	PREDICT-PD r.s.	-0.009	0.002	<0.001	0.991	0.987	0.996	0.025

MDSppPD≤15th, Movement Disorders Society probabilities for prodromal PD with UPSIT ≤15 percentile; r.s., risk score. Sex and age were not included because they are already included in the MDSppPD≤15th and in PREDICT-PD r.s. variables.

DISCUSSION

In this study within two large prospective cohorts, we found that HrQoL, as measured by the EQ-5D-5L and EQ-VAS, is associated with various PD risk factors and overall risk for PD as determined by the MDSppPD and/or the PREDICT-PD r.s. To our knowledge, this is the first study to formally relate quantified PD risk, specifically, the MDSppPD and the PREDICT-PD algorithm, to a preference-based generic health utility (EQ-5D-5L and EQ-VAS) in large, population-recruited at-risk cohorts. It extends work examining which factors associated with higher probabilities of developing PD are associated with lower HrQoL.

This topic is relevant because manifest PD is known to be associated with reduced HrQoL (Barone et al., 2009; Van Munster et al., 2024), as many PD related symptoms such as motor impairment and also mood disorders negatively impact different HrQoL dimensions, including environmental, physical and psychological factors, as well as social interactions, relationships, cognitive functioning, and autonomy (the LIVSFORSK network et al., 2019; The Whoqol Group, 1998). Importantly, HrQoL measures have also increasingly been used for clinical treatment trials. However, whether such effects are also observable in prodromal disease and PD risk cohorts is still unknown.

Our results indicate that both motor symptoms (MDS-UPDRS II^{m}), such as speech and drooling problems, and non-motor symptoms (NMSQ^{m}, MDS-UPDRS Ib^{m}, and PDAQ^{m}), such as daytime sleepiness or constipation problems, are significantly associated with reduced HrQoL at the population level. Importantly, this association is independent of potential confounding factors such as age, sex, education years, and comorbidities. Interestingly, the MDS-UPDRS Ib showed the highest R2 among all the factors in the linear regression analysis across the three Models and both cohorts, indicating that this score (primarily aimed for PD research), explains approximately 25-30% of the variability of the EQ-5D-5L Index. In addition, our findings are also consistent with previous studies in individuals with isolated RBD (Röttgen et al., 2025), which reported lower HrQoL in domains such as vitality, general health, and psychological well-being compared with healthy controls. In contrast, other domains, including emotional role functioning, bodily pain, physical functioning, and physical role functioning, appeared to be relatively preserved compared with patients with PD.

Higher probabilities of prodromal PD were also associated with lower scores on EQ-5D-5L and EQ-VAS. Despite limited research examining HrQoL before the diagnosis of PD, some studies have reported early decline in physical and daily functioning. For example, two large prospective cohorts observed a decline in the physical domain of HrQoL approximately 7.5 years before diagnosis in females and 3.5 years before diagnosis in men (Palacios et al., 2012). Additionally, the Rotterdam study (Darweesh et al., 2017) observed that daily functioning, measured with the Instrumental Activities of Daily Living (IADL), started to decline 7 years before PD diagnosis, while difficulties in the Basic Activities of Daily Living (BADL) appeared 5.4 years before PD diagnosis. These findings align with ours and highlight the potential early deterioration of HrQoL in prediagnostic or prodromal disease phases and the potential of HrQoL as an outcome for symptomatic and disease-modification trials in such early disease phases.

Looking at the EQ-5D-5L domains in the HeBA cohort, higher probabilities of prodromal PD were associated with greater impairment in each EQ-5D-5L domain. In the PREDICT-PD cohort, the directions of association were the same but none of the domains were significantly associated. This

difference could be due to variations in age, comorbidities, years of education and other baseline variables between the two cohorts, as well as the fact that two-thirds of the PREDICT-PD cohort were assessed during or after the COVID-19 pandemic. The pandemic may also have influenced the results, as the stress and restrictions associated with lockdowns may have affected HrQoL across the cohort, making it more difficult to distinguish HrQoL between individuals with high and low probabilities of developing PD. In line with these results, in the PREDICT-PD sample, the higher the estimated PD risk score according to the PREDICT-PD r.s., the higher the impairment in the EQ-5D-5L domains. This is an important addition to the other results, as the PREDICT-PD r.s. includes more risk factors and fewer potential prodromal symptoms, which could have negative consequences for HrQoL.

Although many factors related to PD-risk were associated with HrQoL, smell performance on the UPSIT was an exception, in line with previous studies. Also in the LIFE-Adult-Study (Hinz et al., 2019), no significant correlation was found between olfactory performance and HrQoL, except for the physical activity domain. In contrast, in individuals with chronic severe hyposmia or anosmia, lower olfactory function was associated with lower raw HrQoL scores (Neuland et al., 2011), indicating that smell loss severity may play a role.

Advances in medicine and other factors are leading to increased life expectancy, which means there is a higher risk of developing multiple diseases and/or comorbidities over the course of a lifetime (Marten et al., 2022). These conditions are often associated with functional decline, disability and a lower HrQoL. This was also seen in our sample, where HrQoL was associated with the CCI. Even when adjusting our main analysis for CCI, BMI, education years in addition to age and sex, the associations with subjective symptoms, non-motor symptoms, motor symptoms, and probabilities for prodromal PD remained highly significant. The question is: at what point does a person identify the smallest change as meaningful? The minimal important difference (MID) for the EQ-5D-5L ranges from 0.072 – 0.101 (Henry et al., 2020) across different countries and settings, with the specific information from the German general population indicating a MID of 0.083 (Edward B., 2020) and from the United Kingdom 0.063 (McClure et al., 2017). The results of the linear regression analysis therefore suggest that a conservative MID of 0.09 in the EQ-5D-5L Index would correspond an increase in the MDS-UPDRS Ib of 5 points, in the MDS-UPDRS II of 3 points, or in the MDSppPD of 18%.

The current study has some limitations. First, there is a lack of information regarding the participants' socioeconomic status, as this has been shown to have a significant impact on HrQoL (Hinz et al., 2019). Second, since this was a remote survey, the reliability of the data may be compromised. Third, the HrQoL assessment period (COVID-19 pandemic) in the PREDICT-PD cohort could have influenced the results. Fourth, participants may have reported better HrQoL than the normative population due to a possible selection bias (Supplementary Table 8). Specifically, individuals who were intrinsically motivated to participate may have had higher levels of education and better health status than the general population.

Our study was conducted in population-based cross-sectional samples and there is no data regarding the actual disease status of participants. It could be argued that the predictive value of these probabilities, e.g. >80% defining probable prodromal PD, are not high enough to know that someone is indeed in a prodromal stage of the disease. In fact, high likelihoods markers such as dopaminergic imaging were not available in our study due to the large-scale population-based design. This is, however, to be expected in the light of past similar applications of the MDS criteria in other large population-based cohorts where similar distribution of the probabilities was observed (Giagkou et al., 2020; Mahlknecht et al., 2018). Nonetheless, our main findings were largely consistent across both cohorts conducted in diverse population samples minimizing potential confounding factors and increasing generalizability. To conclude, in this study we present findings in two large cohorts on the

association of probabilities of prodromal PD with HrQoL, the EQ-5D-5L Index and the EQ-VAS. Continuing follow-up examinations of our similar cohorts will show whether HrQoL is indeed compromised in prodromal stages of the disease and will help delineate the trajectories of overall HrQoL and its individual domains.

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DATA AVAILABILITY

All data generated or analysed during this study are included in this published article and its supplementary information files. Additional information can be provided upon reasonable request to the HeBA data access committee.

REFERENCES

Barone, P., Antonini, A., Colosimo, C., Marconi, R., Morgante, L., Avarello, T. P., Bottacchi, E., Cannas, A., Ceravolo, G., Ceravolo, R., Cicarelli, G., Gaglio, R. M., Giglia, R. M., Iemolo, F., Manfredi, M., Meco, G., Nicoletti, A., Pederzoli, M., Petrone, A., … Dotto, P. D. (2009). The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Movement Disorders*, *24*(11), 1641–1649. https://doi.org/10.1002/mds.22643

Berg, D., Postuma, R. B., Adler, C. H., Bloem, B. R., Chan, P., Dubois, B., Gasser, T., Goetz, C. G., Halliday, G., Joseph, L., Lang, A. E., Liepelt-Scarfone, I., Litvan, I., Marek, K., Obeso, J., Oertel, W., Olanow, C. W., Poewe, W., Stern, M., & Deuschl, G. (2015). MDS research criteria for prodromal Parkinson's disease. *Movement Disorders*, *30*(12), 1600–1611. https://doi.org/10.1002/mds.26431

Bestwick, J. P., Auger, S. D., Schrag, A. E., Grosset, D. G., Kanavou, S., Giovannoni, G., Lees, A. J., Cuzick, J., & Noyce, A. J. (2021). Optimising classification of Parkinson's disease based on motor, olfactory, neuropsychiatric and sleep features. *Npj Parkinson's Disease*, *7*(1), 87. https://doi.org/10.1038/s41531-021-00226-2

Bestwick, J. P., Auger, S. D., Simonet, C., Rees, R. N., Rack, D., Jitlal, M., Giovannoni, G., Lees, A. J., Cuzick, J., Schrag, A. E., & Noyce, A. J. (2021). Improving estimation of Parkinson's disease risk—The enhanced PREDICT-PD algorithm. *Npj Parkinson's Disease*, *7*(1), 33. https://doi.org/10.1038/s41531-021-00176-9

Brennan, L., Siderowf, A., Rubright, J. D., Rick, J., Dahodwala, N., Duda, J. E., Hurtig, H., Stern, M., Xie, S. X., Rennert, L., Karlawish, J., Shea, J. A., Trojanowski, J. Q., & Weintraub, D. (2016). The Penn Parkinson's Daily Activities Questionnaire-15: Psychometric properties of a brief assessment of cognitive instrumental activities of daily living in Parkinson's disease. *Parkinsonism & Related Disorders*, *25*, 21–26. https://doi.org/10.1016/j.parkreldis.2016.02.020

Brooks, R. (1996). EuroQol: The current state of play. *Health Policy*, *37*(1), 53–72. https://doi.org/10.1016/0168-8510(96)00822-6

Brumm, M. C., Pierz, K. A., Lafontant, D.-E., Caspell-Garcia, C., Coffey, C. S., Siderowf, A., & Marek, K. (2023). Updated Percentiles for the University of Pennsylvania Smell Identification Test in Adults 50 Years of Age and Older. *Neurology*, *100*(16). https://doi.org/10.1212/WNL.0000000000207077

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases*, *40*(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Chaudhuri, K. R., Yates, L., & Martinez-Martin, P. (2005). The non-motor symptom complex of Parkinson's disease: A comprehensive assessment is essential. *Current Neurology and Neuroscience Reports*, *5*(4), 275–283. https://doi.org/10.1007/s11910-005-0072-6

Darweesh, S. K. L., Verlinden, V. J. A., Stricker, B. H., Hofman, A., Koudstaal, P. J., & Ikram, M. A. (2017). Trajectories of prediagnostic functioning in Parkinson's disease. *Brain*, *140*(2), 429–441. https://doi.org/10.1093/brain/aww291

Dauvilliers, Y., Schenck, C. H., Postuma, R. B., Iranzo, A., Luppi, P.-H., Plazzi, G., Montplaisir, J., & Boeve, B. (2018). REM sleep behaviour disorder. *Nature Reviews Disease Primers*, *4*(1), 19. https://doi.org/10.1038/s41572-018-0016-5

Devlin, N., Finch, A. P., & Parkin, D. (2022). Guidance to Users of EQ-5D-5L Value Sets. In N. Devlin, B. Roudijk, & K. Ludwig (Eds), *Value Sets for EQ-5D-5L* (pp. 213–233). Springer International Publishing. https://doi.org/10.1007/978-3-030-89289-0_5

Devlin, N., Parkin, D., & Janssen, B. (2020). An Introduction to EQ-5D Instruments and Their Applications. In N. Devlin, D. Parkin, & B. Janssen, *Methods for Analysing and Reporting EQ-5D Data* (pp. 1–22). Springer International Publishing. https://doi.org/10.1007/978-3-030-47622-9_1

Doty, R. L., Shaman, P., & Dann, M. (1984). Development of the university of pennsylvania smell identification test: A standardized microencapsulated test of olfactory function. *Physiology & Behavior*, *32*(3), 489–502. https://doi.org/10.1016/0031-9384(84)90269-5

Giagkou, N., Maraki, M. I., Yannakoulia, M., Kosmidis, M. H., Dardiotis, E., Hadjigeorgiou, G. M., Sakka, P., Ntanasi, E., Anastasiou, C. A., Xiromerisiou, G., Stefanis, L., Scarmeas, N., & Stamelou, M. (2020). A Prospective Validation of the Updated Movement Disorders Society Research Criteria for Prodromal Parkinson's Disease. *Movement Disorders*, *35*(10), 1802–1809. https://doi.org/10.1002/mds.28145

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., … LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, *23*(15), 2129–2170. https://doi.org/10.1002/mds.22340

Heinzel, S., Berg, D., Gasser, T., Chen, H., Yao, C., Postuma, R. B., & the MDS Task Force on the Definition of Parkinson's Disease. (2019). Update of the MDS research criteria for prodromal Parkinson's disease. *Movement Disorders*, *34*(10), 1464–1470. https://doi.org/10.1002/mds.27802

Henry, E. B., Barry, L. E., Hobbins, A. P., McClure, N. S., & O'Neill, C. (2020). Estimation of an Instrument-Defined Minimally Important Difference in EQ-5D-5L Index Scores Based on Scoring Algorithms Derived Using the EQ-VT Version 2 Valuation Protocols. *Value in Health*, *23*(7), 936–944. https://doi.org/10.1016/j.jval.2020.03.003

Herdman, M., Gudex, C., Lloyd, A., Janssen, Mf., Kind, P., Parkin, D., Bonsel, G., & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*, *20*(10), 1727–1736. https://doi.org/10.1007/s11136-011-9903-x

Hinz, A., Luck, T., Riedel-Heller, S. G., Herzberg, P. Y., Rolffs, C., Wirkner, K., & Engel, C. (2019a). Olfactory dysfunction: Properties of the Sniffin' Sticks Screening 12 test and associations with quality of life. *European Archives of Oto-Rhino-Laryngology*, *276*(2), 389–395. https://doi.org/10.1007/s00405-018-5210-2

Hinz, A., Luck, T., Riedel-Heller, S. G., Herzberg, P. Y., Rolffs, C., Wirkner, K., & Engel, C. (2019b). Olfactory dysfunction: Properties of the Sniffin' Sticks Screening 12 test and associations with quality of life. *European Archives of Oto-Rhino-Laryngology*, *276*(2), 389–395. https://doi.org/10.1007/s00405-018-5210-2

Ludwig, K., Graf Von Der Schulenburg, J.-M., & Greiner, W. (2018). German Value Set for the EQ-5D-5L. *PharmacoEconomics*, *36*(6), 663–674. https://doi.org/10.1007/s40273-018-0615-8

Mahlknecht, P., Gasperi, A., Djamshidian, A., Kiechl, S., Stockner, H., Willeit, P., Willeit, J., Rungger, G., Poewe, W., & Seppi, K. (2018). Performance of the Movement Disorders Society criteria for prodromal Parkinson's disease: A population-based 10-year study. *Movement Disorders*, *33*(3), 405–413. https://doi.org/10.1002/mds.27281

Marten, O., Brand, L., & Greiner, W. (2022). Feasibility of the EQ-5D in the elderly population: A systematic review of the literature. *Quality of Life Research*, *31*(6), 1621–1637. https://doi.org/10.1007/s11136-021-03007-9

Martinez-Martin, P., & Kurtis, M. M. (2012). Health-related quality of life as an outcome variable in Parkinson's disease. *Therapeutic Advances in Neurological Disorders*, *5*(2), 105–117. https://doi.org/10.1177/1756285611431974

McClure, N. S., Sayah, F. A., Xie, F., Luo, N., & Johnson, J. A. (2017). Instrument-Defined Estimates of the Minimally Important Difference for EQ-5D-5L Index Scores. *Value in Health*, *20*(4), 644–650. https://doi.org/10.1016/j.jval.2016.11.015

Neuland, C., Bitter, T., Marschner, H., Gudziol, H., & Guntinas-Lichius, O. (2011). Health-related and specific olfaction-related quality of life in patients with chronic functional anosmia or severe hyposmia. *The Laryngoscope*, *121*(4), 867–872. https://doi.org/10.1002/lary.21387

Noyce, A. J., Bestwick, J. P., Silveira-Moriyama, L., Hawkes, C. H., Knowles, C. H., Hardy, J., Giovannoni, G., Nageshwaran, S., Osborne, C., Lees, A. J., & Schrag, A. (2014). PREDICT-PD: Identifying risk of Parkinson's disease in the community: methods and baseline results. *Journal of Neurology, Neurosurgery & Psychiatry*, *85*(1), 31–37. https://doi.org/10.1136/jnnp-2013-305420

Palacios, N., Gao, X., Schwarzschild, M., & Ascherio, A. (2012). Declining quality of life in Parkinson disease before and after diagnosis. *Journal of Parkinson's Disease*, *2*(2), 153–160. https://doi.org/10.3233/JPD-2012-12083

Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., Schrag, A.-E., & Lang, A. E. (2017). Parkinson disease. *Nature Reviews Disease Primers*, *3*(1), 17013. https://doi.org/10.1038/nrdp.2017.13

Postuma, R. B., Arnulf, I., Hogl, B., Iranzo, A., Miyamoto, T., Dauvilliers, Y., Oertel, W., Ju, Y., Puligheddu, M., Jennum, P., Pelletier, A., Wolfson, C., Leu-Semenescu, S., Frauscher, B., Miyamoto, M., Cochen De Cock, V., Unger, M. M., Stiasny-Kolster, K., Livia Fantini, M., & Montplaisir, J. Y. (2012). A single-question screen for rapid eye movement sleep behavior disorder: A multicenter validation study. *Movement Disorders*, *27*(7), 913–916. https://doi.org/10.1002/mds.25037

Prasuhn, J., Piskol, L., Vollstedt, E.-J., Graf, J., Schmidt, A., Tadic, V., Tunc, S., Hampf, J., Warrlich, E., Bibergeil, C., Hagenah, J., Klein, C., Kasten, M., & Brüggemann, N. (2017). Non-motor symptoms and quality of life in subjects with mild parkinsonian signs. *Acta Neurologica Scandinavica*, *136*(5), 495–500. https://doi.org/10.1111/ane.12760

Röttgen, S., Lindner, M.-S., Seger, A., Kickartz, J., Weiß, K.-L., Doppler, C. E., Fink, G. R., Ophey, A., & Sommerauer, M. (2025). Non-motor symptoms in prodromal Parkinson's disease are linked to reduced quality of life. *Journal of Parkinson's Disease*, *15*(2), 434–439. https://doi.org/10.1177/1877718X241310726

Rowen, D., Mukuria, C., Bray, N., Carlton, J., Longworth, L., Meads, D., Oluboyede, Y., O'Neill, C., & Yang, Y. (2026). A United Kingdom Value Set for the EQ-5D-5L. *Value in Health*, *29*(5), 858–869. https://doi.org/10.1016/j.jval.2026.03.008

Schade, S., Ghosh, S., Garrido, A., Mahlknecht, P., Marques, T. M., Horlings, C. G. C., Jónsdóttir, S. R., Lang, E., Pauly, C., Rege, K., Schnell, S., Starke, M., Hakelberg, H., Tolosa, E., Trenkwalder, C., Wicke, T., Healthy Brain Ageing (HeBA) Consortium, Bletzacher, G., Djamshidian, A., … Mollenhauer, B. (2025). Identifying individuals at-risk of developing Parkinson's disease using a population-based recruitment strategy: The Healthy Brain Ageing Kassel Study. *Npj Parkinson's Disease*, *11*(1), 216. https://doi.org/10.1038/s41531-025-01008-w

Schuepbach, W. M. M., Rau, J., Knudsen, K., Volkmann, J., Krack, P., Timmermann, L., Hälbig, T. D., Hesekamp, H., Navarro, S. M., Meier, N., Falk, D., Mehdorn, M., Paschen, S., Maarouf, M., Barbe, M. T., Fink, G. R., Kupsch, A., Gruber, D., Schneider, G.-H., … Deuschl, G. (2013). Neurostimulation for Parkinson's Disease with Early Motor Complications. *New England Journal of Medicine*, *368*(7), 610–622. https://doi.org/10.1056/NEJMoa1205158

Siderowf, A., Jennings, D., Eberly, S., Oakes, D., Hawkins, K. A., Ascherio, A., Stern, M. B., Marek, K., & the PARS Investigators. (2012). Impaired olfaction and other prodromal features in the Parkinson At-Risk Syndrome study. *Movement Disorders*, *27*(3), 406–412. https://doi.org/10.1002/mds.24892

Soh, S.-E., Morris, M. E., & McGinley, J. L. (2011). Determinants of health-related quality of life in Parkinson's disease: A systematic review. *Parkinsonism & Related Disorders*, *17*(1), 1–9. https://doi.org/10.1016/j.parkreldis.2010.08.012

the LIVSFORSK network, Haraldstad, K., Wahl, A., Andenæs, R., Andersen, J. R., Andersen, M. H., Beisland, E., Borge, C. R., Engebretsen, E., Eisemann, M., Halvorsrud, L., Hanssen, T. A., Haugstvedt, A., Haugland, T., Johansen, V. A., Larsen, M. H., Løvereide, L., Løyland, B., Kvarme, L. G., … Helseth, S.

(2019). A systematic review of quality of life research in medicine and health sciences. *Quality of Life Research*, *28*(10), 2641–2650. https://doi.org/10.1007/s11136-019-02214-9

The Whoqol Group. (1998). The World Health Organization quality of life assessment (WHOQOL): Development and general psychometric properties. *Social Science & Medicine*, *46*(12), 1569–1585. https://doi.org/10.1016/S0277-9536(98)00009-4

Van Hout, B., Janssen, M. F., Feng, Y.-S., Kohlmann, T., Busschbach, J., Golicki, D., Lloyd, A., Scalone, L., Kind, P., & Pickard, A. S. (2012). Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. *Value in Health*, *15*(5), 708–715. https://doi.org/10.1016/j.jval.2012.02.008

Van Munster, M., Pedrosa, A. J., Künkler, C., & Pedrosa, D. J. (2024). The Quality in Quality of Life in Parkinson's Disease: A Qualitative Meta-Synthesis. *Movement Disorders Clinical Practice*, *11*(7), 761–769. https://doi.org/10.1002/mdc3.14063

Virameteekul, S., Waters, S., Huxford, B., Kuri, A., Tan, M., Pérez-Carbonell, L., Pablo-Fernández, E. D., Schrag, A., Noyce, A. J., & Simonet, C. (2026). PREDICT - PD: A Two-Stage Approach to Early Identification of Parkinson's Disease. *Movement Disorders Clinical Practice*, mdc3.70673. https://doi.org/10.1002/mdc3.70673

Zhao, N., Yang, Y., Zhang, L., Zhang, Q., Balbuena, L., Ungvari, G. S., Zang, Y., & Xiang, Y. (2021). Quality of life in Parkinson's disease: A systematic review and meta-analysis of comparative studies. *CNS Neuroscience & Therapeutics*, *27*(3), 270–279. https://doi.org/10.1111/cns.13549

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