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Normalized Global Parkinson's Symptoms Score: Five-Year Internal Validation in Parkinson's Disease

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Normalized Global Parkinson's Symptoms Score: Five-Year Internal Validation in Parkinson's Disease

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Abstract

Background: Parkinson's disease progression is multidimensional, yet long-term studies commonly report separate motor, non-motor, cognitive, and patient-reported outcomes.

Objectives: To develop and internally validate a normalized Global Parkinson's Symptoms Score (nGPSS) summarizing six clinical domains over five years.

Methods: COPPADIS participants were assessed at baseline and five years. nGPSS equally weighted six 0-100 normalized burden domains: UPDRS-III OFF, UPDRS-IV, Non-Motor Symptoms Scale, Beck Depression Inventory-II, Freezing of Gait Questionnaire, and reversed Parkinson's Disease Cognitive Rating Scale. Validity was examined against PDQ-39 Summary Index, PQ-10, EUROHIS-QOL8, and Schwab and England Activities of Daily Living Scale.

Results: Among 694 baseline participants, 318 had complete nGPSS component data at both visits. nGPSS increased from 16.58 ± 7.62 to 23.25 ± 11.12 (mean change 6.67 ± 8.79; $P<0.001$; standardized response mean 0.76). Change in nGPSS correlated with change in PDQ-39SI (rho=0.582), PQ-10 (rho=-0.239), EUROHIS-QOL8 (rho=-0.460), and ADLS (rho=-0.576; all $P<0.001$). In adjusted models, each 1-SD greater nGPSS worsening was associated with +9.79 PDQ-39SI points and -10.46 ADLS points. AUC for clinically important PDQ-39SI worsening was 0.775.

Conclusions: The nGPSS captured five-year multidomain clinical worsening and showed consistent associations with HRQoL and independence. External validation, reliability assessment, and clinically interpretable change thresholds are required before clinical use.

Parkinson's disease (PD) progression is clinically heterogeneous and extends well beyond deterioration of the motor examination. Motor complications, non-motor manifestations, mood, gait dysfunction, cognition, disability, and patient-perceived quality of life may emerge or worsen at different rates and may become dominant at different stages of disease.[1-5] This multidimensionality is increasingly recognized as a central problem in the selection of clinical outcome assessments for longitudinal cohorts and disease-modifying trials.[6,7] A single conventional scale rarely represents the complete clinical experience of progression, whereas reliance on multiple separate endpoints can make a patient's overall trajectory difficult to summarize.

Longitudinal studies have therefore used combinations of motor, non-motor, cognitive, functional, and patient-reported measures to characterize progression.[4,5,10,11] The prospective Spanish COPPADIS cohort was designed around this comprehensive approach, with repeated multidomain assessments and long-term follow-up.[8,9] Previous COPPADIS analyses showed that non-motor burden, mood, and gait problems are major determinants of quality of life, and that multidomain staging combining motor, non-motor, cognition, and dependency dimensions tracks overall disease severity. [14,26] These observations support the clinical relevance of integrating complementary dimensions rather than interpreting motor progression in isolation.

Composite assessment in PD is not entirely new. The Parkinson's Disease Composite Scale integrates selected motor, non-motor, treatment-complication, and disability items, whereas PARCOMS uses data-driven combinations of Movement Disorder Society-Unified Parkinson's Disease Rating Scale items to enhance sensitivity to progression or treatment effects in defined stages.[12,13] However, a different question is whether full, dedicated instruments representing several clinically important domains can be placed on a common metric and summarized

transparently as a global burden score. We therefore developed the normalized Global Parkinson's Symptoms Score (nGPSS), in which six prespecified domains are directionally aligned, normalized to their theoretical ranges, and equally weighted. The present study aimed to perform an internal five-year evaluation of its cross-sectional construct validity, longitudinal validity, responsiveness, robustness to alternative weighting or domain omission, and discrimination of clinically meaningful health-related quality-of-life worsening. We hypothesized that greater nGPSS burden and worsening would be consistently associated with poorer quality of life and reduced functional independence.

Methods

Study design and participants

This study was a secondary analysis of the prospective, observational, multicenter COPPADIS cohort. The protocol, eligibility criteria, recruitment procedures, participating centers, and scheduled assessments have been described previously.[8,9] The present analysis used the baseline visit (V0) and five-year visit (V60) of participants with PD. The supplied analysis database contained 694 participants coded as patients with PD at V0. The original COPPADIS cohort excluded dementia at baseline and used a broad clinical battery covering motor and non-motor symptoms, cognition, mood, gait, disability, treatment, and quality of life.[8,9]

For the primary longitudinal nGPSS analysis, participants were required to have valid values for all six nGPSS component domains at both V0 and V60. No single-domain imputation was performed because the composite was intended to preserve equal prespecified domain representation. Cross-sectional correlations at V0 and V60 used all participants with a calculable

nGPSS and the relevant external outcome at that visit, so their sample sizes could exceed the complete five-year cohort.

The COPPADIS study was approved by the Comité de Ética de la Investigación Clínica de Galicia, Spain (2014/534; December 2, 2014). Written informed consent was obtained from all participants before study procedures. COPPADIS-2015 was classified by the Agencia Española de Medicamentos y Productos Sanitarios as a post-authorization prospective follow-up study (COH-PAK-2014-01).

Development of the normalized Global Parkinson's Symptoms Score

Six domains were prespecified to capture complementary dimensions of PD burden represented in the original global-symptoms concept: motor impairment, motor complications, global non-motor symptoms, depressive symptoms, freezing of gait, and cognition. Motor impairment and complications were measured with parts III (OFF state) and IV of the original Unified Parkinson's Disease Rating Scale (UPDRS).[15] Non-motor burden was measured with the Non-Motor Symptoms Scale (NMSS), depressive symptoms with the Beck Depression Inventory-II (BDI-II), freezing with the Freezing of Gait Questionnaire (FOGQ), and cognition with the Parkinson's Disease Cognitive Rating Scale (PD-CRS).[16-21]

Because these instruments have markedly different theoretical ranges, direct summation would give greater mathematical influence to scales with larger numerical ranges. Each component was therefore transformed to a 0-100 burden metric using its theoretical range. Cognition was reversed so that higher values uniformly indicated worse status. Equal weighting was chosen a priori for transparency and to avoid deriving weights from the same outcomes used for validation. The score was calculated as: nGPSS = [100×(UPDRS-III/108) + 100×(UPDRS-

IV/23) + 100×(NMSS/360) + 100×(BDI-II/63) + 100×(FOGQ/24) + 100×((134-PD-CRS)/134)]/6. The theoretical nGPSS range is 0-100, with higher values indicating greater multidomain burden. The primary progression variable was ΔnGPSS = nGPSS(V60) - nGPSS(V0); positive values indicate worsening. The conceptual framework and composition of the score are summarized in Figure 1.

External outcome measures

PD-specific health-related quality of life (HRQoL) was assessed with the 39-item Parkinson's Disease Questionnaire Summary Index (PDQ-39SI; 0-100, higher scores worse).[22,23] Global quality of life was evaluated with the patient-rated PQ-10 and the EUROHIS-QOL 8-item index (EUROHIS-QOL8), for which higher values indicate better quality of life; the latter has established cross-cultural psychometric support.[9,24] Functional independence was assessed using the Schwab and England Activities of Daily Living Scale (ADLS; 0-100, higher values greater independence). Longitudinal change for each external outcome was calculated as V60 minus V0. These outcomes were not components of the nGPSS and were selected to provide clinically interpretable external anchors spanning disease-specific HRQoL, global quality of life, and autonomy.

For exploratory discrimination analysis, clinically important PDQ-39SI worsening was defined as an increase of at least 4.22 points, based on published estimates of meaningful deterioration.[28] This binary outcome was used only for receiver operating characteristic analysis and not to define or optimize the nGPSS itself.

Statistical analysis

Continuous variables are summarized as mean ± standard deviation (SD) and, where informative, median and interquartile range; categorical variables are reported as counts and percentages. Cross-sectional construct validity was examined using Spearman rank correlations between nGPSS and PDQ-39SI, PQ-10, EUROHIS-QOL8, and ADLS at V0 and V60. Longitudinal validity was assessed using Spearman correlations between ΔnGPSS and change in each external outcome. Nonparametric bootstrap confidence intervals were calculated for the principal longitudinal correlations. Magnitude and consistency of effect estimates were emphasized rather than statistical significance alone.

Responsiveness to five-year change was summarized with the standardized response mean (SRM), calculated as mean within-person change divided by the SD of change. In accordance with contemporary measurement-property terminology, the SRM was treated as a distribution-based index of change and interpreted together with longitudinal associations with external outcomes rather than as proof of responsiveness in isolation.[29]

Several sensitivity analyses assessed whether results depended on the equal-weighted formulation. First, a baseline-referenced standardized z-score composite was constructed. Second, principal-components analysis (PCA) was applied to standardized, directionally aligned baseline domain scores; the first component and its loadings were examined as supportive structural information and used to derive a PCA-weighted sensitivity score. Third, leave-one-domain-out composites were recalculated to determine whether longitudinal associations with PDQ-39SI or ADLS were driven by a single domain. A consistently specified ratio-based predecessor of the global score was retained as an exploratory comparator for ROC analysis and is detailed in the Supplementary Appendix.

Multivariable linear regression evaluated associations of standardized ΔnGPSS with change in each external outcome. Models used heteroskedasticity-consistent HC3 standard errors and adjusted for the baseline value of the corresponding outcome, age, sex, PD duration, levodopa equivalent daily dose (LEDD), and Hoehn and Yahr stage in the OFF state. Incremental adjusted R2 was calculated relative to the identical covariate model without ΔnGPSS. Discrimination of clinically important PDQ-39SI worsening was summarized by the area under the receiver operating characteristic curve (AUC) with bootstrap confidence intervals; the Youden threshold was considered exploratory. Attrition was evaluated by comparing baseline characteristics of participants included versus not included in the complete longitudinal nGPSS cohort, emphasizing standardized mean differences (SMDs). No multiplicity adjustment was applied to exploratory sensitivity analyses. All tests were two-sided. Analyses were conducted in Python 3.13.5 using pandas 2.2.3, NumPy 2.3.5, SciPy 1.17.0, statsmodels 0.14.6, and scikit-learn 1.8.0. Reporting was structured in accordance with STROBE principles for observational studies.

Results

Participants

Among 694 participants with PD at V0, 318 had complete valid values for all six nGPSS components at both V0 and V60 and comprised the primary longitudinal cohort. Mean age was 62.25 ± 8.42 years, 43.2% were women, mean PD duration was 5.26 ± 4.40 years, and mean UPDRS-III OFF score was 21.55 ± 9.93. Baseline PDQ-39SI was 16.23 ± 12.56 and ADLS was 88.68 ± 9.99 (Table 1).

Cross-sectional construct validity

At V0, nGPSS correlated strongly with PDQ-39SI (rho=0.731; N=607; P<0.001) and moderately with PQ-10 (rho=-0.464), EUROHIS-QOL8 (rho=-0.557), and ADLS (rho=-0.578; all P<0.001). At V60, associations were strong for PDQ-39SI (rho=0.792; N=347) and ADLS (rho=-0.749), moderate-to-strong for EUROHIS-QOL8 (rho=-0.625), and moderate for PQ-10 (rho=-0.473; all P<0.001). Full visit-specific results are provided in Supplementary Table S1.

Five-year change and longitudinal validity

nGPSS increased from 16.58 ± 7.62 at V0 to 23.25 ± 11.12 at V60. Mean within-person change was +6.67 ± 8.79 points (Wilcoxon P<0.001), corresponding to an SRM of 0.76. Greater nGPSS worsening was consistently associated with poorer patient-centered outcomes. ΔnGPSS correlated with ΔPDQ-39SI (rho=0.582; 95% bootstrap CI 0.488-0.661), ΔPQ-10 (rho=-0.239; 95% CI -0.351 to -0.127), ΔEUROHIS-QOL8 (rho=-0.460; 95% CI -0.556 to -0.361), and ΔADLS (rho=-0.576; 95% CI -0.655 to -0.493); all P<0.001 (Table 2). The continuous relationships with PDQ-39SI and ADLS are shown in Figure 2A and 2B, respectively.

Adjusted associations

Associations remained robust after adjustment for the baseline external outcome, age, sex, PD duration, LEDD, and Hoehn and Yahr OFF stage. Each 1-SD greater worsening in ΔnGPSS was associated with a 9.79-point increase in PDQ-39SI (95% CI 8.39-11.18) and a 10.46-point decrease in ADLS (95% CI -11.90 to -9.03). Corresponding associations were -0.62 points for PQ-10 and -2.15 points for EUROHIS-QOL8 (all P<0.001; Table 3). Adding ΔnGPSS increased

adjusted R2 by 0.416 for PDQ-39SI and by 0.422 for ADLS, with smaller but substantial increments for EUROHIS-QOL8 (0.226) and PQ-10 (0.116).

Robustness and discrimination analyses

The first baseline principal component explained 44.5% of total variance. All six domains loaded in the same burden direction; loadings were approximately 0.68 for motor impairment, 0.67 for motor complications, 0.77 for non-motor symptoms, 0.66 for depression, 0.77 for freezing, and 0.39 for cognition (Supplementary Table S3). Baseline-referenced z-score and PCA-weighted composites showed longitudinal associations with external outcomes similar to, or slightly stronger than, the equal-weighted nGPSS. In leave-one-domain-out analyses, the association with ΔPDQ-39SI remained significant after omission of any single domain (rho 0.501-0.598), as did the association with ΔADLS (absolute rho 0.477-0.583; Supplementary Table S4).

Among 314 participants with paired PDQ-39SI values, 157 met the prespecified criterion for clinically important worsening. ΔnGPSS yielded an AUC of 0.775 (bootstrap 95% CI 0.720-0.825). The ratio-based predecessor yielded an AUC of 0.728 (Figure 3; Supplementary Table S6). The ΔnGPSS threshold maximizing Youden's index was approximately +6.5 points, with sensitivity 0.650 and specificity 0.803; this data-derived threshold was considered exploratory rather than a clinical cutoff.

Attrition

Participants in the complete five-year cohort were broadly similar to those not included with respect to age, disease duration, LEDD, cognition, baseline HRQoL, and ADLS. Completers had modestly milder baseline motor severity, with SMDs of approximately -0.24 for Hoehn and Yahr

OFF stage and -0.20 for UPDRS-III OFF. Other baseline SMDs were small (Supplementary Table S5), suggesting limited but non-negligible attrition toward a somewhat milder motor phenotype.

Discussion

In this multicenter five-year cohort, the nGPSS provided a transparent summary of change across six clinically complementary PD domains and demonstrated convergent evidence of validity against multiple external outcomes. Four findings are particularly relevant. First, the score increased substantially over five years, with an SRM of 0.76. Second, nGPSS showed strong cross-sectional associations with PD-specific HRQoL and functional independence and moderate associations with global quality of life. Third, change in nGPSS tracked change in all four external outcomes and remained strongly associated with PDQ-39SI and ADLS after adjustment for baseline status and relevant clinical covariates. Fourth, the findings were not dependent on a single domain or a single weighting strategy. Together, these results support the nGPSS as a research-oriented measure of multidomain clinical burden trajectory, while falling short of the external validation required for routine clinical use.

The rationale for a multidomain measure is grounded in the natural history of PD. Progression does not occur along a single clinical axis, and rates of deterioration in motor function, cognition, gait, non-motor symptoms, and disability differ between individuals and across disease stages.[3-5,10,11] Consensus work on clinically meaningful progression has emphasized outcomes that matter to patients and caregivers, and current initiatives for disease-modifying trials similarly highlight the challenge of choosing outcomes that are valid, sensitive to change, practical, and reflective of the lived experience of progression.[4,6] The recent Movement Disorder Society review of clinical

outcome assessments further illustrates the breadth of constructs currently measured in PD and the continuing need to match instruments to the intended construct.[7] The nGPSS is intended to address a specific part of this problem: summarizing broad clinical burden across domains, not replacing domain-specific assessments when the research question concerns a particular symptom or mechanism.

Our approach also differs from existing composite strategies. The Parkinson's Disease Composite Scale selects 17 items spanning motor signs, non-motor manifestations, treatment complications, and disability to provide a relatively brief global scale.[12] PARCOMS, in contrast, derives stage-specific weighted combinations of MDS-UPDRS items intended to improve responsiveness for progression or treatment-effect detection.[13] COPPADIS work using the MNCD classification has pursued yet another strategy by staging patients across motor, non-motor, cognition, and dependency axes.[14] The nGPSS does not compete directly with these tools: it preserves the information contained in six full instruments and produces a continuous summary after transforming them to a common metric. This may be useful in deeply phenotyped observational cohorts or secondary analyses in which the component instruments have already been collected, but it necessarily carries greater assessment burden than a purpose-built bedside composite.

Normalization was a central methodological choice. Simply adding raw totals from instruments ranging from 0-23 to 0-360 would create implicit weights determined largely by numerical scale range. Transforming each component to 0-100 makes that arithmetic explicit and gives each prespecified domain equal theoretical influence. Equal weighting has the advantages of simplicity, reproducibility, and avoidance of outcome-driven overfitting, but it remains a clinical assumption rather than an empirically proven optimum. The sensitivity analyses are therefore

288 important: the z-score and PCA-weighted approaches led to similar conclusions, and omission of
289 any single domain did not abolish the associations with HRQoL or ADLS. The PCA finding that
290 cognition loaded less strongly than the other domains should not be interpreted as evidence that
291 cognition is unimportant. Rather, it is consistent with partial independence of cognitive
292 trajectories from other clinical dimensions and with the concept of the nGPSS as a multidomain
293 formative composite rather than a strictly unidimensional latent scale. Measurement-property
294 frameworks distinguish these questions and caution against equating a single internal-structure
295 statistic with overall validity.[29]
296 The associations with HRQoL and autonomy were clinically coherent. Non-motor symptoms,
297 depression, and freezing of gait are established major contributors to poor quality of life in PD,
298 including in COPPADIS.[25-27] Patient-centered qualitative work also shows that quality of life
299 reflects a broad interaction between symptoms, function, autonomy, social participation, and
300 adaptation rather than motor severity alone.[31] Accordingly, a global clinical-burden score would
301 be expected to correlate with PDQ-39SI and ADLS if it captures clinically relevant progression.
302 At the same time, this relationship should not be overinterpreted as complete independence of
303 constructs: PDQ-39 contains mobility, emotional, cognitive, and bodily-discomfort domains, and
304 therefore shares conceptual content with several nGPSS components. The inclusion of two
305 global quality-of-life measures and ADLS provides useful triangulation, but future validation
306 against external clinical milestones, objective mobility measures, digital outcomes, caregiver
307 outcomes, or biomarker-supported progression would reduce the risk of criterion overlap.
308 The longitudinal results provide stronger evidence than cross-sectional correlation alone. A 1-SD
309 greater increase in nGPSS was associated with approximately 9.8 points of PDQ-39SI worsening
310 and 10.5 points of ADLS decline after covariate adjustment, and the incremental adjusted R2

exceeded 0.40 for both outcomes. These effect sizes indicate that the composite captures a large proportion of between-patient variation in long-term change in HRQoL and independence in this cohort. The SRM of 0.76 also indicates substantial standardized change over five years, but distribution-based responsiveness statistics do not by themselves establish meaningful change.[29] Likewise, the AUC of 0.775 for PDQ-39SI deterioration supports group-level discrimination, whereas the +6.5-point nGPSS Youden threshold is sample-derived and should not be used as a patient-level cutoff. Published PDQ-39 estimates of clinically important worsening provided a useful anchor for this exploratory analysis,[28] but a clinically interpretable nGPSS threshold ultimately requires prospective anchor-based validation in an independent sample.

A potential application is longitudinal research in which investigators want one prespecified global clinical endpoint while retaining the ability to examine individual domains secondarily. This could reduce fragmented interpretation caused by multiple parallel scales and may be useful for cohort stratification or exploratory analyses of treatments expected to affect several dimensions. However, the nGPSS should not be interpreted as a biomarker of neurodegeneration. Over five years, observed changes reflect disease biology together with symptomatic treatment, treatment complications, comorbidity, aging, measurement error, and adaptation. Even OFF-state motor assessments can remain influenced by long-duration treatment effects, and longitudinal cohorts such as the Parkinson's Progression Markers Initiative demonstrate that treatment initiation complicates interpretation of clinical rating-scale trajectories.[11] The score is therefore best described as a measure of multidomain clinical burden progression rather than a direct measure of underlying neuropathologic progression.

Several limitations are important. First, this is development and internal longitudinal validation within a single national cohort; external validation is essential, particularly in populations with

different age, disease duration, ethnicity, healthcare context, and treatment patterns. Second, complete-case analysis reduced the primary longitudinal sample to 318 participants. Attrition differences were generally small but indicated somewhat milder baseline motor severity among completers, which could attenuate or alter progression estimates. Third, the study was not designed to establish all measurement properties of a new clinical outcome assessment. Test-retest reliability, measurement error, minimal detectable change, inter-rater effects, and prospective interpretability were not assessed. Fourth, the score uses the original UPDRS rather than the contemporary MDS-UPDRS. The MDS-UPDRS has different content and clinimetric structure, and its parts are generally interpreted as distinct dimensions rather than indiscriminately summed.[30] A future nGPSS implementation should therefore be prospectively mapped and validated using contemporary measures rather than assuming direct interchangeability. Fifth, dementia was excluded at COPPADIS baseline, potentially restricting the cognitive spectrum and contributing to the weaker PCA loading for cognition. Sixth, normalization by theoretical range prevents range-driven weighting but does not equalize empirical variance, reliability, or clinical importance across domains. Finally, some conceptual overlap exists among NMSS, BDI-II, FOGQ, and the external HRQoL measures; although leave-one-domain-out analyses were reassuring, independent anchors are needed.

These results nevertheless provide a strong rationale for the next validation step. An external cohort should prespecify the six-domain algorithm, evaluate reliability and measurement error, repeat the longitudinal validity analyses, and test whether the score predicts meaningful milestones such as sustained loss of independence, falls, cognitive deterioration, institutionalization, or escalation of treatment. Contemporary MDS-based motor assessments and repeated intervals shorter than five years should be examined, and alternative weighting

strategies should be compared without optimizing them on the same validation outcomes. Until those studies are completed, the nGPSS should be regarded as an internally validated research composite rather than a routine clinical scale. Within that scope, the present findings show that a normalized multidomain score can summarize five-year PD clinical burden and capture changes that are closely linked to HRQoL and functional independence.

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Author Roles

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique. Diego Santos García: 1A, 1B, 1C, 2A, 2B, 3A. Rest of the coauthors: 1C, 3B.

Disclosures

Ethical Compliance Statement

The study was approved by the Comité de Ética de la Investigación Clínica de Galicia, Spain (2014/534; December 2, 2014). Written informed consent was obtained from all participants before study procedures. COPPADIS-2015 was classified by the Agencia Española de Medicamentos y Productos Sanitarios as a post-authorization prospective follow-up study (COH-PAK-2014-01). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability

The COPPADIS protocol and statistical analysis plan are available on reasonable request. Deidentified participant-level data are not publicly available for legal and ethical reasons. Requests regarding access should be directed to the study principal investigator in accordance with COPPADIS governance.

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533

Figure Legends and Supplemental File Legend

Figure 1. Conceptual framework and composition of the normalized Global Parkinson's Symptoms Score (nGPSS). Six prespecified domains are normalized to a common 0-100 burden metric and equally weighted; higher values indicate greater multidomain clinical burden.

Figure 2. Longitudinal association between five-year change in nGPSS and patient-centered outcomes. Change in nGPSS versus change in PDQ-39 Summary Index (A) and Schwab and England Activities of Daily Living Scale (B). Positive ΔnGPSS indicates worsening.

Figure 3. Discrimination of clinically important PDQ-39 Summary Index worsening. Receiver operating characteristic curves compare ΔnGPSS with the ratio-based predecessor score; corresponding AUCs were 0.775 and 0.728, respectively.

Supplementary Appendix. Supplementary methods note and Tables S1-S7 provide cross-sectional validity, responsiveness, weighting, attrition, discrimination, and predecessor-comparator sensitivity analyses.

Appendix 1. COPPADIS Study Group

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Sánchez Díez, Gema	Hospital Universitario Ramón y Cajal, Madrid, Spain	Site investigator	Evaluation of participants and/or data management
Sánchez Ferro, Álvaro	Hospital Universitario 12 de Octubre, Madrid, Spain	Site investigator	Management, dissemination and collaboration
Sánchez Peláez, Maria Victoria	Hospital Universitario Marqués de Valdecilla, Santander, Spain	Site investigator	Evaluation of participants and/or data management
Sancho Valderrama, Beatriz	Complejo Asistencial Universitario de Burgos, Burgos, Spain	Site investigator	Evaluation of participants and/or data management
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Sierra Peña, María	Hospital Universitario Marqués de Valdecilla, Santander, Spain	Site investigator	Evaluation of participants and/or data management
Solano, Berta	Institut d'Assistència Sanitària (IAS) - Instituí Cátala de la Salud. Girona, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Solleiro Vidal, Ángela	CHUAC, Complejo Hospitalario Universitario de A Coruña	Study coordinator	Review and monitoring database
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Torres Moral, Alejandro	Hospital Universitario Virgen Macarena, Sevilla, Spain	Site investigator	Evaluation of participants and/or data management
Valero, Caridad	Hospital Arnau de Vilanova, Valencia, Spain	Site investigator/PI	Evaluation of participants and/or data management
Valero García, María Fuensanta	Hospital Universitario Son Espases, Palma de Mallorca, Spain	Site investigator	Evaluation of participants and/or data management
Vela, Lydia	Fundación Hospital de Alcorcón, Madrid, Spain	Site investigator / PI	Coordination at the center Evaluation of participants and/or data management
Vives Pastor, Bárbara	Hospital Universitario Son Espases, Palma de Mallorca, Spain	Site investigator	Evaluation of participants and/or data management

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Table 1. Baseline characteristics of the primary longitudinal cohort.

Variable	N	Value
Age, years	318	62.2 ± 8.4
Disease duration, years	305	5.3 ± 4.4
LEDD, mg/day	317	545.3 ± 373.0
H&Y OFF	315	1.9 ± 0.5
UPDRS III OFF	318	21.6 ± 9.9
UPDRS IV	318	1.9 ± 2.2
NMSS	318	44.6 ± 37.5
BDI-II	318	8.3 ± 7.1
FOGQ	318	3.4 ± 4.3
PD-CRS	318	91.6 ± 15.4
PDQ-39SI	318	16.2 ± 12.6
PQ-10	317	7.3 ± 1.6
EUROHIS-QOL8	317	30.4 ± 4.2
ADLS	318	88.7 ± 10.0
Female sex, n (%)	317	137 (43.2)

Values are mean ± SD unless otherwise indicated. ADLS, Schwab and England Activities of Daily Living Scale; BDI-II, Beck Depression Inventory-II; FOGQ, Freezing of Gait Questionnaire; LEDD, levodopa equivalent daily dose; NMSS, Non-Motor Symptoms Scale; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PDQ-39SI, 39-item Parkinson's Disease Questionnaire Summary Index; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 2. Longitudinal validity of change in the normalized Global Parkinson's Symptoms Score.

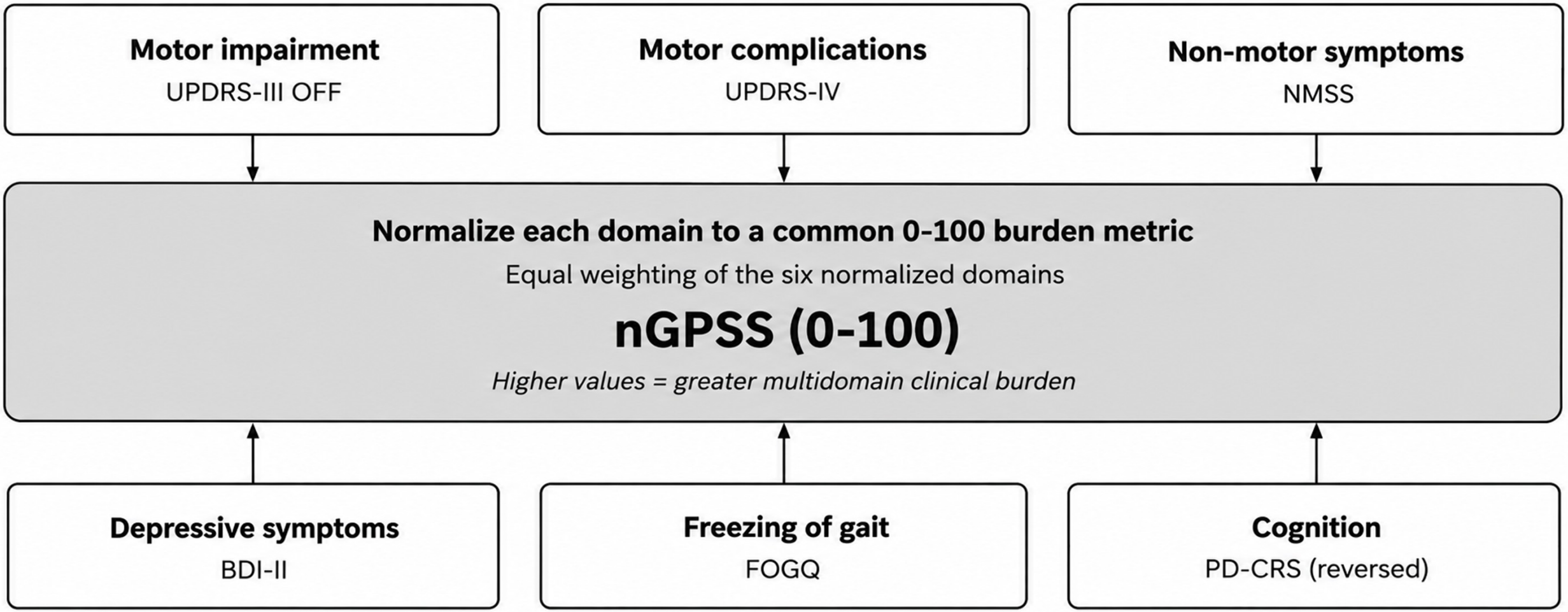
External outcome	N	Spearman rho	95% bootstrap CI	P
ΔPDQ-39SI	314	0.582	0.488 to 0.661	<0.001
ΔPQ-10	317	-0.239	-0.351 to -0.127	<0.001
ΔEUROHIS-QOL8	317	-0.460	-0.556 to -0.361	<0.001
ΔADLS	318	-0.576	-0.655 to -0.493	<0.001

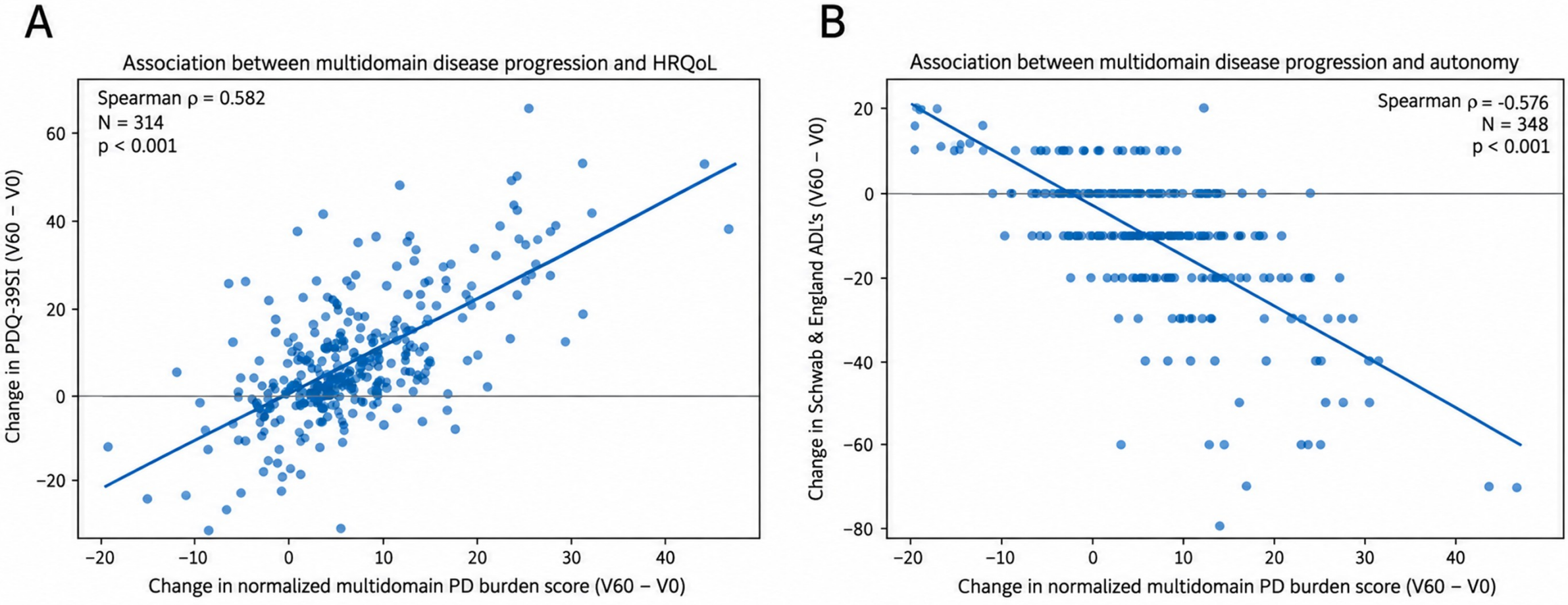
Change is V60 minus V0. Positive ΔPDQ-39SI indicates worse health-related quality of life; negative changes in PQ-10, EUROHIS-QOL8, and ADLS indicate worsening. ADLS, Schwab and England Activities of Daily Living Scale; CI, confidence interval; PDQ-39SI, 39-item Parkinson's Disease Questionnaire Summary Index.

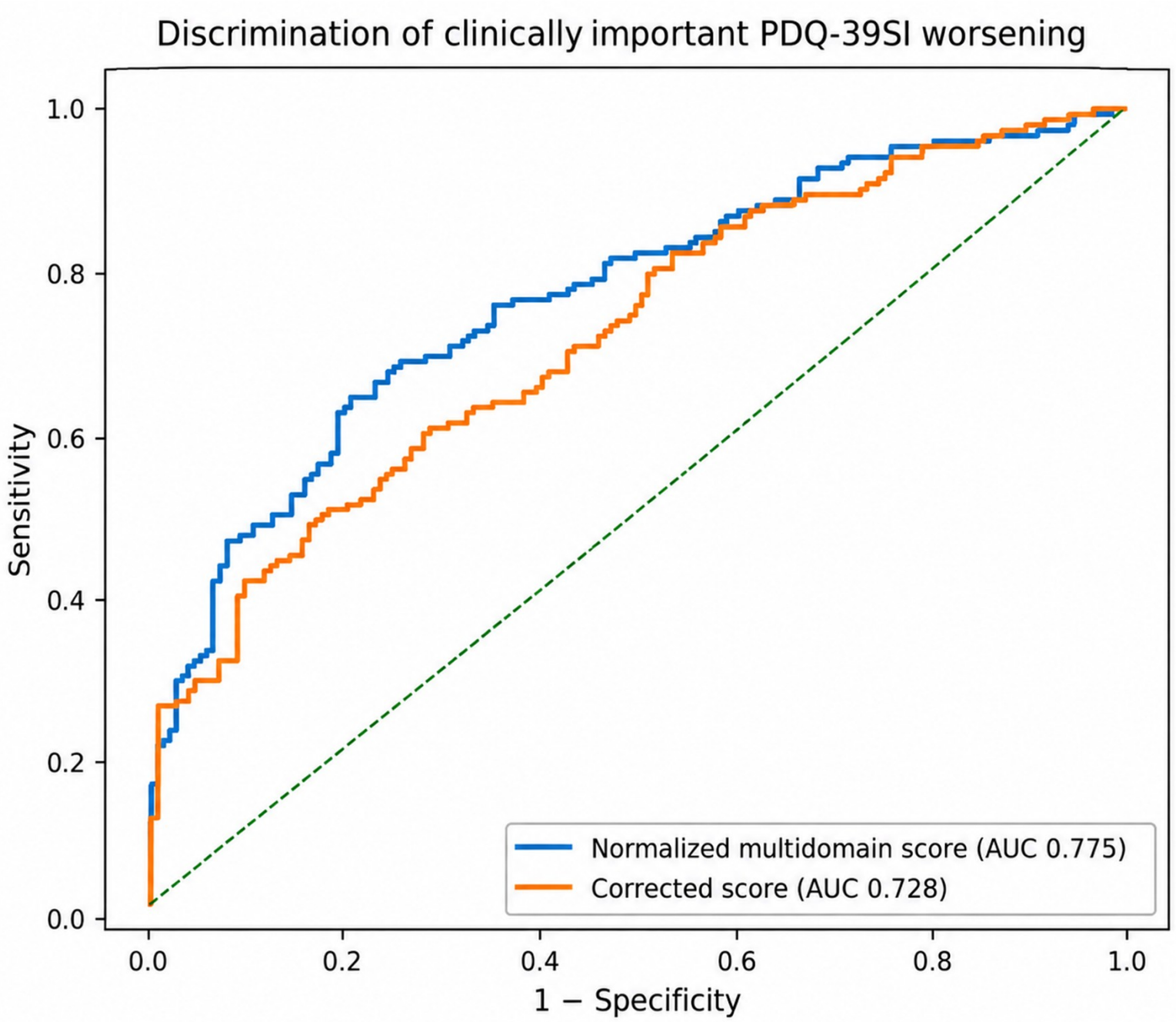
Table 3. Multivariable association of normalized score worsening with five-year change in external outcomes.

Outcome	N	β per 1-SD ΔnGPSS	95% CI	P	Adjusted R2	ΔAdjusted R2
ΔPDQ-39SI	296	+9.79	8.39 to 11.18	<0.001	0.493	0.416
ΔPQ-10	300	-0.62	-0.78 to -0.45	<0.001	0.348	0.116
ΔEUROHIS-QOL8	300	-2.15	-2.60 to -1.70	<0.001	0.336	0.226
ΔADLS	300	-10.46	-11.90 to -9.03	<0.001	0.486	0.422

Models adjust for baseline value of the external outcome, age, sex, Parkinson's disease duration, levodopa equivalent daily dose, and Hoehn and Yahr stage in the OFF state, with HC3 robust standard errors. ΔAdjusted R2 is the increment over the covariate model without ΔnGPSS. CI, confidence interval; nGPSS, normalized Global Parkinson's Symptoms Score.


Motor impairment
UPDRS-III OFF
Motor complications
UPDRS-IV
Non-motor symptoms
NMSS
Normalize each domain to a common 0-100 burden metric
Equal weighting of the six normalized domains
nGPSS (0-100)
Higher values = greater multidomain clinical burden
Depressive symptoms
BDI-II
Freezing of gait
FOGQ
Cognition
PD-CRS (reversed)


A
Association between multidomain disease progression and HRQoL
Spearman ρ = 0.582
N = 314
p < 0.001
Change in PDQ-39SI (V60 – V0)
Change in normalized multidomain PD burden score (V60 – V0)
B
Association between multidomain disease progression and autonomy
Spearman ρ = -0.576
N = 348
p < 0.001
Change in Schwab & England ADL's (V60 – V0)
Change in normalized multidomain PD burden score (V60 – V0)


Discrimination of clinically important PDQ-39SI worsening
Sensitivity
1 − Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Normalized multidomain score (AUC 0.775)
Corrected score (AUC 0.728)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- COPPADISnGPSSJNTSupplementaryAppendixd1.docx