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NEUROEPIDEMIOLOGY OF PARKINSON'S DISEASE IN AN URBAN AREA OF IRAN

From screening and prevalence to nutritional, clinical and psychiatric features and quality of life

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Karolinska Institutet

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Cover picture: It has been designed, drawn and colored by *Seyed-Mohammad Fereshtehnejad*. The tulip was first recognized as a symbol for Parkinson's disease in 1980, when a Dutch horticulturalist named *J.W.S. Van der Wereld* decided to honor *Dr. James Parkinson*, the first person to describe Parkinson's in 1817, by naming a tulip after him. It thus became a symbol for Parkinson's disease. In this symbolic painting, some tulips are colored representing people with parkinsonism who were screened, and the uncolored ones resemble the false negative cases or the patients who were not recruited in the sampling procedure of the screening phase of this doctoral project. Different shapes of the tulips, various formats of coloring and dissimilar sizes all represent the broad heterogeneity between Parkinson's disease patients that has been shown in the last study of this project. The design of the whole painting that reminds a Persian carpet and the inverted tulips that bloom in the Iranian plateau, all symbolize the study setting.

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Neuroepidemiology of Parkinson's Disease in an Urban Area of Iran

From screening and prevalence to nutritional, clinical and psychiatric features and quality of life

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Stockholm 2015

To my loving parents

&

To all people with Parkinson's disease

ABSTRACT ENGLISH

Background. Parkinson's disease (PD) is the second most common neurodegenerative disorder with complex presentations consisting of different motor and non-motor symptoms. The multisystem and progressive nature of PD has made it a complicated entity with broad variation in manifestations and reciprocal effects on several aspects of daily life.

Aims. This doctoral thesis investigated different neuroepidemiologic aspects of PD and parkinsonism including its screening and prevalence in the urban area of Tehran, Iran, nutritional status and risk factors for malnutrition, clinical and psychiatric features, health-related quality of life (HRQoL) and its determinants in Iranian PD patients. For this purpose, we also aimed to validate several questionnaires and make a new screening instrument.

Study I. Psychometric properties of the Persian-translated version of the short-form Parkinson's disease questionnaire (PDQ-8) were assessed in 114 Iranian patients with PD consecutively recruited from an outpatient Movement Disorder Clinic. The Cronbach's alpha coefficient of the entire PDQ-8 was 0.740 (95% CI: 0.661-0.806). Replacement of PDQ-8 items with other questions with the highest internal consistency within each dimension of the long-form PDQ (PDQ-39) did not further improve reliability. The Persian version of the PDQ-8 was shown to be a valid and reliable instrument to assess HRQoL in Iranian PD population especially in mental and behavioral aspects. PDQ-8 is a practical and informative instrument in daily clinical practice where clinicians are in shortage of time and need a validated self-reported brief questionnaire.

Study II. To develop a new instrument for screening of parkinsonism in community-based surveys, a comprehensive questionnaire consisting of 25 items on different PD symptoms was filled in 157 patients with parkinsonism and 110 controls. Using the concept of clinical utility index (CUI), six items on "*stiffness & rigidity*", "*tremor & shaking*", "*troublesome buttoning*", "*troublesome arm swing*", "*feet stuck to floor*" and "*slower daily activity*" demonstrated good validity (CUI$\geq$0.64) to be included in the new screening tool. We introduced a new set of six items to screen parkinsonism, which showed higher diagnostic values [area under curve (AUC)=0.977] compared to the previously developed questionnaires. This new instrument could be used in population-based surveys to screen parkinsonism in poor-resource settings.

Study III. Following a random multistage sampling of the households within the network of "*Health Centers*" with 374 subunits in all 22 urban districts of Tehran, 20,621 individuals answered the baseline checklist and the screening questionnaire developed in *study II*. Data from 19,500 persons aged $\geq$30 years were entered in the final analysis. A total number of 157 cases were positively screened for parkinsonism that resulted in age- and sex-adjustment prevalence rates of 222.9/100,000 (95% CI: 160-300) and 285/100,000 (95% CI: 240-329) based on the real Tehran population and "*WHO World Standard Population*", respectively. The male/female ratio of probable parkinsonism was 1.62 and there was a steady increase by advancing age. The calculated rates for the prevalence of parkinsonism in our study are closer to the reports from some European and Middle-East countries, higher than reports from the Eastern Asian and African populations, and lower than Australia. The prevalence rate of >200/100,000 for parkinsonism in Tehran, Iran is considered as a medium-to-high rate.

Study IV. Nutritional status was evaluated in 143 Iranian PD patients and 145 age- and sex-matched controls by means of the validated Persian version of the mini-nutritional assessment (MNA). The mean of total MNA score was not significantly different between the two groups [24.4 (SD=3.8) in controls vs. 25.1 (SD=3.4) in PD patients, p=0.094]. Three (2.1%) PD patients were suffering from malnutrition and another 37 (25.9%) were at risk of

malnutrition; while in control group similar feature was observed (2.0% malnourished and 35.2% at risk of malnutrition, p=0.228). Our findings indicated similar nutritional status among mild-to-moderate PD patients and matched controls from the same community. However, nearly one third of PD population were either malnourished or at risk of malnutrition necessitating more attention towards nutritional assessment in PD.

Study V. Factors affecting nutritional status were investigated in 150 PD patients including a comprehensive list of motor and non-motor scales. The total score of the Unified Parkinson's disease rating scale (UPDRS) scale (r=-0.613, p<0.001) and PD duration (r=-0.284, p=0.002) had a significant inverse correlation with the total MNA score. A higher Hoehn and Yahr stage [2.5 vs. 2.0, p<0.001], more severe anxiety [8.8 vs. 5.9, p=0.002], depression [9.0 vs. 3.6, p<0.001] and fatigue [5.4 vs. 4.2, p<0.001] were observed in PD patients with nutritional insufficiency. Except for stigma, all other domains of the HRQoL significantly correlated with the total MNA score. We showed that disease duration, severity of motor and psychiatric symptoms (depression, anxiety) and fatigue associated with nutritional status in PD, which itself affected different aspects of HRQoL especially the emotional well-being and mobility.

Study VI. A broad spectrum of demographic, motor and non-motor characteristics were evaluated in 157 PD patients consisting of comorbidity profile, nutritional status, UPDRS (total items), psychiatric symptoms (depression, anxiety), fatigue and psychosocial functioning through physical examination, validated questionnaires and scales. Structural equation model (SEM) and multivariate regressions were applied to find determinants of Parkinson's disease severity index (PDSI) and different domains of HRQoL (PDQ-39). Female sex, anxiety, depression and UPDRS-part II scores were the significant independent determinants of PDSI. A structural model consisting of global motor, global non-motor and co-morbidity indicator as three main components was able to predict 89% of the variance in HRQoL. However, outstanding heterogeneities in the pattern and determinants of HRQoL were found among different PD phenotypes.

Conclusions. We showed a medium-to-high prevalence rate for suspicious parkinsonism in Iranian population living in the urban area of Tehran by means of a novel 6-item screening instrument. Similar nutritional status was found in mild-to-moderate PD patients and matched controls from the same community. Yet, approximately one third of people with mild-to-moderate PD were either malnourished or at risk of malnutrition. Duration of PD, severity of motor symptoms, depression, anxiety and fatigue associated with nutritional status in PD patients. Motor symptoms affecting activities of daily living (ADL), depression, anxiety and female sex were found to be the strongest independent determinants of HRQoL in Iranian PD population. Clear heterogeneities were found in the pattern and determinants of HRQoL in different PD phenotypes, which should be considered during the assessments and developing personalized interventions to improve life quality in PD patients with different prominent features.

Keywords. *Parkinson's disease, Parkinsonism, Neuroepidemiology, Validation, Reliability, Psychometric properties, Health-related quality of life, Screening instrument, Diagnostic value, Prevalence, Community-based, Door-to-door study, Nutritional status, Malnutrition, Determinant factor, Motor symptom, Non-motor symptom, Psychiatric features, Anxiety, Depression, Fatigue, Phenotype, Heterogeneity*

ABSTRACT SWEDISH

Bakgrund. Parkinsons sjukdom (PS) är den näst vanliga neurodegenerativa sjukdomen med komplexa sjukdomsyttringar bestående av olika motoriska och icke-motoriska symtom. Den komplexa och progressiva karaktären av PS har medfört att det finns en bred variation av olika sjukdomsmanifestationer och även de effekter som de kan ha på det dagliga livet.

Målsättning. Denna doktorsavhandling har undersökt olika neuroepidemiologiska aspekter av PS och parkinsonism inkluderande screening och prevalensundersökning i huvudstaden Teheran, Iran, nutritionsstatus och riskfaktorer för malnutrition, somatiska och psykiatriska symtom, hälsorelaterad livskvalitet (HRQoL) och dess determinanter hos iranska PS-patienter. För detta ändamål validerades också flera frågeformulär och ett nytt screeninginstrument utvecklades.

Studie I. Psykometriska egenskaper hos den persiska versionen av kortformen av frågeformuläret ”Parkinson’s Disease Questionnaire” (PDQ-8) genomfördes på 114 iranska patienter med PS, konsekutivt rekryterade från en neurologisk motorikenhet. Cronbach alpha koefficienten för hela PDQ-8 var 0.740 (95% CI: 0.661-0.806). Vid utbyte av frågor från PDQ-8 med andra frågor med den högsta interna konsistensen inom varje dimension av långversionen av frågeformuläret (PDQ-39), förbättrade inte reliabiliteten. Den persiska versionen av PDQ-8 visade sig vara valid och utgöra ett reliabelt instrument för att bedöma HRQoL i en iransk PS-population, särskilt vad det gäller mentala och beteendemässiga aspekter. PDQ-8 är ett praktiskt och informativt instrument för dagligt kliniskt bruk där läkare ofta har brist på tid och behöver ett validerat, självrapporterande, kort frågeformulär.

Studie II. Utvecklandet av ett nytt instrument för screening av parkinsonism i populationsstudier togs fram genom att sammanställa 25 frågor om olika PS symtom. Formuläret fylldes i av 157 patienter med parkinsonism och 110 kontroller. Genom att använda konceptet ”Clinical Utility Index” (CUI), uppvisade 6 frågor god validitet (CUI≥0.64) och kunde inkluderas i det nya screeninginstrumentet. De nyintroducerade frågorna för att screena för parkinsonism var: ”*stelhet och rigiditet*”, ”*skakningar*”, ”*svårt att knäppa knappar*”, “*dålig armpendling*”, ”*fastnande med fötterna*”, ”*besvär med dagliga aktiviteter*”. Formuläret visade högre diagnostiska värden (area under curve; AUC=0.977) jämfört med tidigare utvecklade frågeformulär. Detta nya instrument skulle därmed kunna användas för att screena för parkinsonism i populationsbaserade studier i resurssvaga områden.

Studie III. Genom att använda en slumpmässig flerstegsmetod och rekrytera personer från olika hushåll inom ett nätverk kallat ”Health Centers” med 374 enheter inom alla Teherans 24 stadsdistrikt, kunde 20,621 personer besvara en checklista och det frågeformulär som utvecklats i Studie II. Av dessa personer kunde data från 19,500 personer >30 år inkluderas i den slutliga analysen. Totalt 157 personer screenade positivt för parkinsonism, vilket resulterade i ålders- och könsjusterade prevalenssiffror om 222.9/100,000 och 285/100,000 baserat på den uppgivna Teheranska populationen respektive WHO World Standard Population. Könsrelationen man/kvinna för sannolik parkinsonism var 1.62 och det var en ökning med ökande ålder. De kalkylerade siffrorna för prevalensen av parkinsonism i vår studie liknar de siffror i rapporter från vissa Europeiska och MellanÖstern länder men är högre än siffror från Östasien och Afrikanska populationer och lägre än de från Australien. Prevalenssiffran på >200/100,000 för parkinsonism i Teheran, Iran, får anses som en medel/hög siffra.

Studie IV. Nutritionsstatus utvärderades hos 143 iranska PS-patienter och 145 ålders- och könsmatchade kontroller genom att använda den validerade persiska versionen av mini-nutritional assessment (MNA). Medelvärdet av totala MNA poängen var inte signifikant skiljd mellan grupperna (24.4; SD=3.8 för kontroller mot 25.1; SD=3.4 hos PS patienter;

p=0.094). Tre (2.1 %) PS patienter uppvisade malnutrition och ytterligare 37 (25.9%) var i riskzonen för malnutrition. Motsvarande siffror i kontrollgruppen var 2.0% malnutrierade och 35.2% med risk för malnutrition (*p*=0.228). Våra fynd indikerar likartat nutritionsstatus hos patienter med mild /moderat sjukdomsgrad av PS och matchade kontroller från samma område. Dock var nästan en tredjedel av PS populationen malnutrierad eller i riskzonen för malnutrition, vilket pekar på att man bör vara uppmärksam på nutritionsbedömningar vid PS.

Studie V. Faktorer som påverkar nutritionsstatus undersöktes hos 150 PS-patienter genom en omfattande genomgång av motoriska och icke-motoriska skalor. Den totala poängen från frågeformuläret ”Unified Parkinson’s Disease Rating Scale” (UPDRS) (r=-0.613; *p*<0.001) och PS-durationen (r=-0.284; *p*=0.002) uppvisade en signifikant omvänd korrelation med totala MNA poängen. Högre stadier av Hoehn och Yahr [2.5 vs. 2.0; *p*<0.001], svår oro [8.8 vs. 5.9; *p*=0.002], depression [9.0 vs. 3.6; *p*<0.001] och fatigue [5.4 vs. 4.2; *p*<0.001] observerades hos PS-patienterna med nutritionsbrist. Förutom stigma korrelerade alla andra domäner i HRQoL signifikant med totala MNA poängen. Vi visade att sjukdomsduration, svårighetsgrad av motoriska och psykiatriska symtom (oro, depression) och fatigue var associerade med PS patienternas nutritionsstatus, som påverkade olika aspekter av HRQoL och särskilt emotionellt välbefinnande och rörlighet.

Studie VI. Ett brett spektrum av demografiska, motoriska och icke-motoriska variabler utvärderades genom fysisk undersökning och validerade frågeformulär hos 157 PS patienter. Dessa bestod av komorbiditet,, nutritionsstatus, UPDRS, psykiatriska symtom(depression, oro), fatigue och psykosocial funktion. Statistiska metoder med ”Structural equation model” (SEM) och multivariat regression användes för att hitta determinanter till ”Parkinson´s disease severity index” (PDSI) och olika domäner av HRQoL (PDQ-39). Kvinnligt kön, oro, depression och UPDRS del II var signifikant oberoende determinanter för PDSI. En strukturerad modell bestående av globalt motoriska, globalt icke-motoriska och komorbiditets indikatorer som de tre huvudkomponenterna kunde predicera 89 % av variansen i HRQoL. Dock var olika heterogeniteter i mönstret och determinanterna för HRQoL olika för olika fenotyper av PD.

Konklusion. Vi har påvisat en medel/hög prevalens för suspekt parkinsonism i en Iransk population som bor i Teherean genom att använda ett nyutvecklat 6-frågors screening formulär. Samma nutritionsstatus förelåg hos mild/moderat svårighetsgrad av PS och matchade kontroller från samma område. Ändock var en tredjedel av personerna med mild/moderat PS antingen malnutrierade eller i riskzonen för malnutrition. PS durationen, svårighetsgraden av motoriska symtomen, depression, oro och fatigue var associerade med nutritionsstatus vid PS. Motoriska symtom som påverkar dagliga aktiviteter (ADL), depression, oro och kvinnligt kön var de starkaste oberoende determinanterna för HRQoL i en Iransk PS population. Olika heterogeniteter fanns i mönstret och determinanterna för HRQoL hos olika fenotyper av PS. Detta bör uppmärksammas vid bedömningar och vid användandet av individualiserade interventione för att förbättra livskvaliteten hos PS patienter med olika fenotyper.

ABSTRACT PERSIAN

پیش‌زمینه: بیماری پارکینسون دومین اختلال نورودژنراتیو شایع است که تظاهراتی بسیار متنوع شامل علایم مختلف حرکتی و غیرحرکتی دارد. طبیعت پیشرونده و چندسیستمی پارکینسون، آن‌را به یک بیماری پیچیده با ناهمخوانی بسیار در تظاهرات بین بیماران مختلف بدل کرده که می‌تواند اثرات متقابلی بر جنبه‌های گوناگون زندگی روزمره‌ی بیماران داشته باشد.

اهداف: در این پروژه جنبه‌های گوناگون نورواپیدمیولوژیک بیماری پارکینسون و پارکینسونیسم در حوزه‌ی شهری تهران در کشور ایران مورد بررسی قرار گرفته است که عبارتند از: غربالگری و شیوع، وضعیت تغذیه‌ای، تظاهرات بالینی و روانشناختی، کیفیت زندگی مرتبط با سلامت و تعیین‌کننده‌های آن در بیماران ایرانی مبتلا به پارکینسون. همچنین، اعتبار پرسشنامه‌های متعدد مورد استفاده در این پروژه در پژوهش‌هایی جداگانه مورد ارزیابی قرار گرفته و ابزار غربالگری جدیدی نیز ساخته شد.

پژوهش ۱: ویژگی‌های سایکومتریک نسخه‌ی فارسی و کوتاه شده‌ی پرسشنامه‌ی Parkinson's disease questionnaire (PDQ-8) در ۱۱۴ بیمار ایرانی مبتلا به پارکینسون که به‌طور متناوب و به‌روش نمونه‌گیری غیر احتمالی آسان از مراجعین به کلینیک اختلالات حرکتی انتخاب شده بودند، مورد بررسی قرار گرفت. ضریب آلفای کرونباخ برای نسخه-ی فارسی پرسشنامه‌ی PDQ-8 معادل (۰/۸۰۶-۰/۶۶۱ :حدود اطمینان ۹۵٪) ۰/۷۴۰ محاسبه گردید. جایگزینی آیتم‌های پرسشنامه‌ی PDQ-8 با سوالاتی دیگر که دارای بالاترین همبستگی درونی در هر بعد محتوایی پرسشنامه‌ی اصلی (PDQ-39) بودند منجر به ارتقای پایایی پرسشنامه‌ی PDQ-8 نگردید. در این پژوهش، نسخه‌ی فارسی و کوتاه شده‌ی پرسشنامه‌ی PDQ-8 به‌عنوان یک ابزار معتبر و پایا برای سنجش کیفیت زندگی مرتبط با سلامت به‌ویژه در جنبه‌های روانی و رفتاری در بیماران ایرانی مبتلا به پارکینسون معرفی شد. این پرسشنامه‌ی کوتاه می‌تواند به‌عنوان یک ابزار کاربردی در معاینات روتین بالینی بیماران پارکینسون و هنگامی‌که پزشک به‌علت کوتاهی زمان نیازمند ابزاری مختصر و دقیق برای سنجش کیفیت زندگی بیماران است مورد استفاده قرار بگیرد.

پژوهش ۲: برای ساختن ابزار غربالگری جدید پارکینسونیسم در مطالعات جمعیتی، پرسشنامه‌ی جامعی مشتمل بر ۲۵ سوال استاندارد در مورد علایم مختلف این بیماری در ۱۵۷ فرد مبتلا به پارکینسونیسم و ۱۱۰ فرد شاهد تکمیل گردید. با استفاده از شاخص کارایی بالینی یا Clinical Utility Index (CUI) شش علامت شامل: "*سفتی و ریژیدیتی عضلانی*"، "*ترمور و لرزش*"، "*اشکال در بستن دگمه‌ها*"، "*اشکال در حرکات هماهنگ دست‌ها در حین راه رفتن*"، "*احساس چسبیدن پاها به زمین*" و "*کندی فعالیت‌های روزمره*" به‌عنوان بهترین آیتم‌ها با اعتبار خوب (CUI ≥۰/۶۴) برای انتخاب جهت غربالگری پارکینسونیسم معرفی شدند. این پژوهش منجر به معرفی یک پرسشنامه‌ی غربالگری جدید برای پارکینسونیسم گردید که در مقایسه با موارد مشابه قبلی بهترین ارزش تشخیصی (Area Under Curve =۰/۹۷۷) را نشان داد. این ابزار می‌تواند در مطالعات جمعیتی برای غربالگری اولیه‌ی افراد مشکوک به پارکینسونیسم به‌ویژه در جوامع فاقد نظام‌های ثبت بیماری مورد استفاده قرار گیرد.

پژوهش ۳: طی نمونه‌گیری تصادفی چند مرحله‌ای از خانوارهای ساکن در تمام ۲۲ منطقه‌ی شهری تهران و از طریق شبکه‌ی خانه‌های سلامت محله شامل ۳۷۴ واحد، تعداد ۲۰۶۲۱ فرد مورد بررسی قرار گرفتند. در هر یک از افراد چک‌لیست اطلاعات زمینه‌ای و پرسشنامه‌ی جدید غربالگری ساخته شده در *پژوهش ۲* تکمیل می‌گردید و در نهایت داده‌های مربوط به ۱۹۵۰۰ نفر با سن >۳۰ سال مورد آنالیز نهایی قرار گرفت. پس از بررسی، ۱۵۷ نفر مشکوک به پارکینسونیسم غربالگری شدند که بر این اساس شیوع استاندارد شده بر مبنای توزیع سنی و جنسی در جمعیت واقعی تهران معادل (۳۰۰-۱۶۰ :حدود اطمینان ۹۵٪) ۲۲۲/۹ در هر ۱۰۰۰۰۰ نفر و بر مبنای "*جمعیت استاندارد سازمان جهانی بهداشت* (WHO)" معادل (۳۲۹-۲۴۰ :حدود اطمینان ۹۵٪) ۲۸۵ در هر ۱۰۰۰۰۰ نفر تخمین زده شد. نسبت جنسی مرد/زن در افراد غربالگری شده‌ی پارکینسونیسم احتمالی ۱/۶۲ بود و شیوع به‌صورت پیوسته با بالا رفتن گروه سنی افزایش می‌یافت. شیوع تخمین زده شده برای پارکینسونیسم احتمالی در این پژوهش به آمارهای برخی کشورهای اروپایی و خاورمیانه نزدیک بوده ولی از گزارشات شیوع در کشورهای آسیای شرقی و آفریقایی بالاتر و از برآوردها در استرالیا پایین‌تر است. به هر روی نرخ شیوع >۲۰۰ در هر ۱۰۰۰۰۰ نفر برای پارکینسونیسم در نواحی شهری تهران در ایران به‌عنوان شیوعی متوسط-به-بالا در نظر گرفته می‌شود.

پژوهش ۴: وضعیت تغذیه‌ای در ۱۴۳ بیمار ایرانی مبتلا به پارکینسون و ۱۴۵ فرد شاهد جور شده از نظر سن و جنس با استفاده از نسخه‌ی فارسی و معتبر شده‌ی پرسشنامه‌ی Mini-Nutritional Assessment (MNA) مورد مقایسه قرار گرفت. تفاوت آماری معنی‌داری در میانگین امتیاز کلی MNA بین دو گروه وجود نداشت [در گروه بیماران: (SD=۳/۴) ۲۵/۱ و در گروه شاهد: (SD=۳/۸) ۲۴/۴، (p=۰/۰۹۴)]. در گروه بیماران پارکینسون ۳ نفر (۲/۱٪) با سوء تغذیه و ۳۷ نفر (۲۵/۹٪) با خطر سوء تغذیه شناسایی شدند که البته تفاوت معنی‌داری با گروه شاهد نداشت (p=۰/۲۲۸). هر چند نتایج این پژوهش به‌طور کلی نشان‌دهنده‌ی وضعیت تغذیه‌ای مشابهی بین بیماران مبتلا به پارکینسون با شدت خفیف تا متوسط و گروه شاهد بود، باید در نظر داشت که نزدیک به یک سوم بیماران به‌نوعی دچار مشکل تغذیه‌ای بودند که لزوم توجه بیشتر به ارزیابی تغذیه‌ای افراد مبتلا به بیماری پارکینسون را نشان می‌دهد.

پژوهش ۵: عوامل موثر بر وضعیت تغذیه‌ای در ۱۵۰ بیمار مبتلا به پارکینسون با ارزیابی جامعی از علایم حرکتی و غیر حرکتی مورد بررسی قرار گرفت. نمره‌ی کلی مقیاس جامع امتیازگذاری بیماری پارکینسون یا Unified Parkinson's disease rating scale (UPDRS) ($r= -۰/۶۱۳$ ،$p<۰/۰۰۱$) و مدت زمان ابتلا به پارکینسون ($r= -۰/۲۸۴$ ،$p=۰/۰۰۲$) همبستگی معنی‌دار معکوسی با نمره‌ی کلی MNA داشتند. بیماران دچار عدم کفایت تغذیه‌ای به‌طور معنی‌داری در مرحله‌ی بالاتر بیماری با Hoehn and Yahr stage ($p<۰/۰۰۱$ ،۲/۵ در مقابل ۲/۰)، اضطراب ($p=۰/۰۰۲$ ،۸/۸ در مقابل ۵/۹)، افسردگی ($p<۰/۰۰۱$ ،۹/۰ در مقابل ۳/۶) و خستگی شدیدتری ($p<۰/۰۰۱$ ،۵/۴ در مقابل ۴/۲) در مقایسه با بیماران دارای وضعیت تغذیه‌ای مناسب بودند. به‌جز استیگما، سایر حیطه‌های کیفیت زندگی مرتبط با سلامت به‌طور معنی‌داری با امتیاز کلی MNA ارتباط داشت. نتایج این پژوهش نشان داد مدت زمان بیماری، شدت علایم حرکتی و طیف گسترده‌ای از علایم غیرحرکتی و روانشناختی با وضعیت تغذیه‌ای بیماران پارکینسون مرتبط می‌باشد که می‌تواند به‌طور قابل توجهی کیفیت زندگی بیماران را در جنبه‌های مختلف به‌ویژه احساسی و حرکتی تحت تاثیر قرار دهد.

پژوهش ۶: به‌منظور دستیابی به مدل ساختاری یا Structural Equation Modeling (SEM) مناسب برای الگوی کیفیت زندگی مرتبط با سلامت در بیماری پارکینسون، طیف گسترده‌ای از ویژگی‌های زمینه‌ای (وضعیت تغذیه‌ای و بیماری-های زمینه‌ای)، علایم حرکتی (UPDRS) و غیرحرکتی (علایم روانشناختی، خستگی، عملکرد روانی-اجتماعی) در ۱۵۷ بیمار مبتلا به پارکینسون توسط پرسشنامه‌های معتبر، مقیاس‌های استاندارد و معاینات بالینی مورد ارزیابی قرار گرفت. در آنالیز چندمتغیره‌ی رگرسیونی، جنسیت زن، اضطراب، افسردگی و نمره‌ی UPDRS-part II فاکتورهای تاثیرگذار مستقل بر شاخص شدت بیماری پارکینسون یا Parkinson's disease severity index (PDSI) شناخته شدند. مدل معتبر SEM شامل نشانگرهای جامعی برای علایم حرکتی، غیرحرکتی و بیماری‌های همراه موفق به پیشگویی ۸۹٪ از تغییرات کیفیت زندگی مرتبط با سلامت در بیماری پارکینسون گردید. جالب آن‌که این مدل ساختاری در زیر گروه‌های مختلف بیماران پارکینسون با فنوتیپ‌های متفاوت، الگوها و عوامل تعیین‌کننده‌ی متفاوتی داشت که بیانگر ناهمگونی قابل توجه بین بیماران پارکینسون است.

نتیجه‌گیری: در این پروژه شیوعی متوسط-به-بالا برای پارکینسونیسم احتمالی در جمعیت ایرانی ساکن در مناطق شهری تهران با استفاده از یک ابزار غربالگری جدید و معتبر نشان داده شد. وضعیت تغذیه‌ای بیماران مبتلا به پارکینسون با شدت خفیف-تا-متوسط با گروه شاهد جور شده از همان جامعه مشابه بود. با این‌حال، نزدیک به یک سوم این بیماران علی‌رغم شدت نسبتا کم بیماری پارکینسون در معرض سوء تغذیه قرار داشتند. مدت زمان بیماری، شدت علایم حرکتی، افسردگی، اضطراب و خستگی با وضعیت تغذیه‌ای در بیماران مبتلا به پارکینسون در ارتباط بود. همچنین علایم حرکتی موثر بر فعالیت‌های روزمره، جنسیت زن، افسردگی و اضطراب به‌عنوان قوی‌ترین عواملی که مستقلا بر کیفیت زندگی مرتبط با سلامت در بیماران ایرانی مبتلا به پارکینسون تاثیر می‌گذارند، شناخته شدند. ناهمگونی آشکاری در الگوها و عوامل تعیین‌کننده‌ی کیفیت زندگی مرتبط با سلامت در بیماران پارکینسون با فنوتیپ‌های مختلف دیده شد. این هتروژنیتی می‌بایست در ارزیابی، روند درمان و سایر مداخلات برای ارتقای علایم و کیفیت زندگی بیماران پارکینسون با فنوتیپ‌ها و علایم مختلف مد نظر قرار گیرد تا سرانجام منجر به تکامل و به‌کارگیری روش‌های انفرادی موثر (Personalized approach) در هر یک از بیماران شود.

LIST OF SCIENTIFIC PAPERS

(Included in PhD project)

I. **Fereshtehnejad SM**, Naderi N, Rahmani A, Shahidi GA, Delbari A, Lökk J Psychometric study of the Persian short-form eight-item Parkinson's disease questionnaire (PDQ-8) to evaluate health related quality of life (HRQoL.)
Health Qual Life Outcomes 2014; 12: 78

II. **Fereshtehnejad SM**, Shafieesabet M, Rahmani A, Farhadi F, Hadizadeh H, Shahidi GA, Delbari A, Lökk J. A novel 6-item screening questionnaire for parkinsonism: validation and comparison between different instruments.
Neuroepidemiology 2014; 43(3-4): 178-93

III. **Fereshtehnejad SM**, Shafieesabet M, Rahmani A, Delbari A, Lökk J. Medium-to-high prevalence of screening-detected parkinsonism in the urban area of Tehran, Iran: data from a community-based door-to-door study.
Neuropsychiatr Dis Treat 2015; 11: 1–12

IV. **Fereshtehnejad SM**, Ghazi L, Sadeghi M, Khaefpanah D, Shahidi GA, Delbari A, Lökk J. Prevalence of malnutrition in patients with Parkinson's disease: a comparative study with healthy controls using Mini Nutritional Assessment (MNA) questionnaire.
J Parkinsons Dis 2014; 4(3): 473-481

V. **Fereshtehnejad SM**, Ghazi L, Shafieesabet M, Shahidi GA, Delbari A, Lökk J. Motor, psychiatric and fatigue features associated with nutritional status and its effects on quality of life in Parkinson's disease patients.
PLoS One 2014; 9(3): e91153

VI. **Fereshtehnejad SM**, Shafieesabet M, Farhadi F, Hadizadeh H, Rahmani A, Naderi N, Khaefpanah D, Shahidi GA, Delbari A, Lökk J. Heterogeneous determinants of quality of life in different phenotypes of Parkinson’s disease.
Submitted Manuscript

LIST OF OTHER SCIENTIFIC PAPERS DURING DOCTORAL EDUCATION

(Not included in PhD project)

I. **Fereshtehnejad SM**, Delbari A, Lökk J. Methods for assessing mortality in Parkinson's Disease Surveys.
Mov Disord. 2012; 27(7): 926

II. Lökk J, **Fereshtehnejad SM**. Managing palliative care in Parkinson's disease from diagnosis to end-stage disease: what the clinician should know.
Neurodegen Dis Manage. 2013; 3: 169-183

III. **Fereshtehnejad SM**, Hadizadeh H, Farhadi F, Shahidi GA, Delbari A, Lökk J. Reliability and validity of the Persian version of the fatigue severity scale (FSS-Per) in idiopathic Parkinson's disease patients.
Parkinsons Dis. 2013; 2013: 935429

IV. **Fereshtehnejad SM**, Religa D, Westman E, Aarsland D, Lökk J, Eriksdotter M. Demography, diagnostics, and medication in dementia with Lewy bodies and Parkinson's disease with dementia: data from the Swedish Dementia Quality Registry (SveDem).
Neuropsychiatr Dis Treat. 2013; 9: 927-935

V. **Fereshtehnejad SM**, Lökk J. Orthostatic hypotension in patients with Parkinson's disease and atypical parkinsonism.
Parkinsons Dis. 2014; 2014: 475854

VI. **Fereshtehnejad SM**, Johnell K, Eriksdotter M. Anti-dementia drugs and co-medication among patients with Alzheimer's disease : investigating real-world drug use in clinical practice using the Swedish Dementia Quality Registry (SveDem).
Drugs Aging. 2014; 31(3): 215-24

VII. Eriksson H, **Fereshtehnejad SM**, Falahati F, Farahmand B, Religa D, Eriksdotter M. Differences in routine clinical practice between early and late onset Alzheimer's disease: data from the Swedish Dementia Registry (SveDem).
J Alzheimers Dis. 2014; 41(2): 411-9

VIII. Faxén-Irving G, **Fereshtehnejad SM**, Falahati F, Cedergren L, Göranzon H, Wallman K, García-Ptacek S, Eriksdotter M, Religa D. Body Mass Index in Different Dementia Disorders: Results from the Swedish Dementia Quality Registry (SveDem).
Dement Geriatr Cogn Dis Extra. 2014; 4(1): 65-75

IX. **Fereshtehnejad SM**, Farhadi F, Hadizadeh H, Shahidi GA, Delbari A, Lökk J. Cross-cultural validity, reliability, and psychometric properties of the Persian version of the scales for outcomes in Parkinson's disease-psychosocial questionnaire.
Neurol Res Int. 2014; 2014: 260684

X. Cermakova P, **Fereshtehnejad SM**, Johnell K, Winblad B4, Eriksdotter M, Religa D. Cardiovascular medication burden in dementia disorders: a nationwide study of 19,743 dementia patients in the Swedish Dementia Registry.
Alzheimers Res Ther. 2014; 6(3): 34

XI. Falahati F, **Fereshtehnejad SM**, Religa D, Wahlund LO, Westman E, Eriksdotter M. The Use of MRI, CT and Lumbar Puncture in Dementia Diagnostics: Data from the SveDem Registry.
Dement Geriatr Cogn Disord. 2014; 39(1-2): 81-91

XII. **Fereshtehnejad SM**, Lökk J. Active aging for individuals with Parkinson's disease: definitions, literature review, and models.
Parkinsons Dis. 2014; 2014: 739718

XIII. **Fereshtehnejad SM,** Damangir S, Cermacova P, Aarsland D, Eriksdotter M, Religa D. Comorbidity profile in dementia with Lewy bodies versus Alzheimer's disease: a linkage study between the Swedish Dementia Registry and the Swedish National Patient Registry.
Alzheimers Res Ther. 2014; 6: 65

XIV. **Fereshtehnejad SM,** Hadizadeh H, Farhadi F, Shahidi GA, Delbari A, Lökk J. Comparison of the psychological symptoms and disease-specific quality of life (QoL) between early- and typical-onset Parkinson's disease patients.
Parkinsons Dis. 2014; 2014: 819260

XV. Shams S, Martola J, Granberg T, Li X, Shams M, **Fereshtehnejad SM**, Cavallin L, Aspelin P, Kristoffersen-Wiberg M, Wahlund LO. Cerebral microbleeds: different prevalence, topography and risk factors depending on dementia diagnosis: the Karolinska Imaging Dementia Study.
AJNR Am J Neuroradiol. 2015; 36(4): 661-6

XVI. Cermakova P, Lund LH, **Fereshtehnejad SM**, Johnell K, Winblad B, Dahlström U, Eriksdotter M, Religa D. Heart failure and dementia: survival in relation to types of heart failure and different dementia disorders.
Eur J Heart Fail. 2015 [Epub ahead of print]

XVII. Ghazi L, **Fereshtehnejad SM**, Abbasi Fard S, Sadeghi M, Shahidi GA, Lökk J. Mini Nutritional Assessment (MNA) is rather a reliable and valid instrument to assess nutritional status in both Iranian healthy adults and elderly with a chronic disease.
Ecol Food Nutr. 2015; 25: 1-16

XVIII. Religa D, **Fereshtehnejad SM**, Cermakova P, Edlund AK, Garcia Ptacek S, Granqvist N et al. SveDem, the Swedish Dementia Registry - a tool for improving the quality of diagnostics, treatment and care of dementia patients in clinical practice.
PLoS One. 2015; 10(2): e0116538

XIX. **Fereshtehnejad SM,** Shafieesabet M, Shahidi GA, Delbari A, Lökk J. Restless legs syndrome in patients with Parkinson's disease: a comparative

study on prevalence, clinical characteristics, quality of life and nutritional status.
Acta Neurol Scand. 2015; 131(4): 211-8

XX. Naghavi M, Wang H, Lozano R, …, **Fereshtehnejad SM**, …, Murray C (GBD 2013 Mortality and Causes of Death Collaborators). Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.
Lancet. 2015; 385(9963): 117-71

XXI. Rios Romenets S, Anang J, **Fereshtehnejad SM**, Pelletier A, Postuma RB. Tango for treatment of motor and non-motor manifestations in Parkinson's disease: A Randomized control study.
Complement Ther Med. 2015; 23(2): 175-84

XXII. **Fereshtehnejad SM**, Rios Romenets S, Anang J, Latreille V, Gagnon JF, Postuma RB. New Clinical subtypes of Parkinson's disease and longitudinal disease progression: A prospective cohort comparison with other phenotypes.
JAMA Neurology [Accepted]

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of daily living
ANOVA	Analysis of variance
AP	Atypical parkinsonism
AUC	Area under curve
BHSQ	Baylor Health Screening Questionnaire
BIC	Bayesian information criterion
BMI	Body mass index
CBD	Corticobasal degeneration
CC	Calf circumference
CFI	Comparative Fit Index
CI	Confidence interval
COMT	Catechol o-methyltransferase
CUI	Clinical utility index
CV	Coefficient of variation
ET	Essential tremor
FCRDC	Firoozgar Clinical Research Development Center
FSS	Fatigue severity scale
GBD	Global burden of disease
HADS	Hospital anxiety and depression scale
HRQoL	Health-related quality of life
ICD	Impulse control disorder
IPD	Idiopathic Parkinson's disease
IQR	Interquartile range
LB	Lewy body
MAC	Mid arm circumference
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
MNA	Mini-nutritional assessment
MSA	Multiple system atrophy
MUST	Malnutrition universal screening tool
NFI	Normed Fit Index
NMS	Non-motor symptom

NMSS	Non-motor symptoms scale of Parkinson's disease
NPV	Negative predictive value
OH	Orthostatic hypotension
OR	Odds' ratio
PD	Parkinson disease
PDQ	Parkinson's disease questionnaire
PDSI	Parkinson's disease summary index
PPV	Positive predictive value
PSP	Progressive supranuclear palsy
QoL	Quality of life
RBD	Rapid eye movement sleep behavior disorder
REM	Rapid eye movement
RMSEA	Root Mean Square Error of Approximation
ROC	Receiver operating characteristics
SCOPA-PS	Scales for outcomes in Parkinson's disease-psychosocial questionnaire
SD	Standard deviation
SEM	Structural equation model
SGA	Subjective global assessment
SNES	Sicilian neuro-epidemiology study
SNpc	Substantia nigra pars compacta
SRW	Standardized regression weight
TLI	Tucker-Lewis Index
UPDRS	Unified Parkinson's disease rating scale
VIF	Variance inflation factor
WHO	World health organization
YRS	Year

1 INTRODUCTION

1.1 Parkinson's disease

1.1.1 Definitions and diagnostic criteria

Parkinson's disease (PD) is considered as the major neurodegenerative movement disorder conventionally characterized by its cardinal motor symptoms namely bradykinesia, resting tremor, rigidity and postural instability [1]. The *United Kingdom Brain Bank* has introduced the following criteria for parkinsonian syndrome [2], which has long been used in both clinical practice and research projects as well:

- "*Bradykinesia*
- *At least one of the following:*
    - *muscular rigidity*
    - *4-6 Hz rest tremor*
    - *postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction*" [2]

Recent profound changes in knowledge and improvements in the understanding of PD have emerged the International Parkinson and Movement Disorders Society (MDS) to commission a task force to redefine PD [3]. Increasingly more and more non-motor symptoms (NMS) such as psychiatric disorders, cognitive impairment, autonomic dysfunction, sleep disorders and sensory problems have been found to be associated with PD, some of which have been recognized as prodromal symptoms that might even appear before motor manifestations start [4]. Not only in symptomatology but also in pathophysiology of PD, new findings have deeply changed our previous knowledge such as genetic cases without synucleinopathy and rather considerable prevalence of incidental Lewy body (LB) deposition in elderly population [3]. Yet, the mainstay of PD definition is based on motor features and the MDS task force commission in 2014, highlighted clinical expertise as the gold standard for PD diagnosis, which consists of the following criteria [3]:

- "*A motor clinical syndrome, with levodopa-responsive parkinsonism, typical clinical characteristics, and the absence of markers suggestive of other disease*
- *Pathologic confirmation of α-synuclein deposition and dopamine neuronal loss in the substantia nigra pars compacta (SNpc)*" [3]

1.1.2 Etiology and pathology

Idiopathic Parkinson's disease (IPD), also called PD, is the most common type of a larger group of movement disorders called parkinsonism. About 30-40% of the patients with parkinsonism suffer from other types generally labeled as atypical parkinsonism (AP) [5-6]. Although these entities largely overlap in symptoms, different underlying pathologies are involved. Other than vascular and drug-induced parkinsonism and those with consequential disease following stroke, inflammation and intoxication, no clear single etiology has been found for other types of parkinsonism including the commonest one, IPD. A complex etiology has now been proposed consisting of both genetic and environmental factors. Some of the gene mutations that could cause PD both in familial and sporadic forms are *α-synuclein*, *Parkin*, *SNCA*, *UCHL1*, *DJ1*, *PINK1*, *GIGYF2* and *LRRK2* [7-8], yet only 15% of the patients with PD have a positive history of parkinsonism in their first-degree relatives [9]. Among the environmental risk factors, some pesticides and chemicals such as *1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine* (MPTP) [10], bacterial infections (*Gardnerella vaginalis*, *Helicobacter jejuni*) [8] and head injuries [11] have been proposed. Nevertheless, aging is well known as the strongest risk factor for development of PD [8].

The hallmark of PD pathology is the accumulation of misfolded α-synuclein protein, its deposition and formation of the LBs in susceptible neurons, especially in the SNpc, which leads to the loss of dopaminergic neurons [12]. Death of dopaminergic neurons may itself initiates a cascade of adverse events namely energy crisis, oxidative stress, inflammatory reactions by glial cells, proteasomal abnormalities, finally protein aggregation and α-synuclein deposition [8]. Nonetheless, PD has now been accepted as a progressive multiorgan disease with a comprehensive list of non-motor features indicating that non-dopaminergic systems such as serotonergic and cholinergic are also involved in pathophysiology of the NMS [4, 13]. So far, different hypotheses have been proposed on how synucleinopathy starts, spreads and presents in PD pathophysiologic cascade. According to the *Braak* theory, LB pathology firstly involves the *Meissner* and *Auerbach* plexus of the foregut, then through a retrograde trans-synaptic transmission reaches the preganglionic parasympathetic motor neurons of the vagus nerve, spreads up to the olfactory bulb and medulla oblongata, then further up to substantia nigra and lastly to higher cortical levels [14-15]. This theory fairly corresponds to the chronicity of the symptoms in most PD patients starting from a non-motor prodromal phase, to motor manifestations and ending with developed emotional and cognitive dysfunctions (*Figure 1*). Furthermore, there are other proofs of concept such as the finding of neuronal synuclein deposition in 60–70% of the colon biopsies from PD patients [16].

The "*prion-like*" hypothesis has been also proposed as a potential mechanism to explain the spreading of synucleinopathy in PD. Accordingly, pathogenic misfolded α-synuclein can be released by living neurons through exocytosis into the neighboring extracellular milieu, where it is then taken up by the intact nearby neurons via endocytosis. This exogenous α-synuclein may act as a template that endorses misfolding of endogenous α-synuclein to ultimately form LB in the second chain of the neurons [17-18].

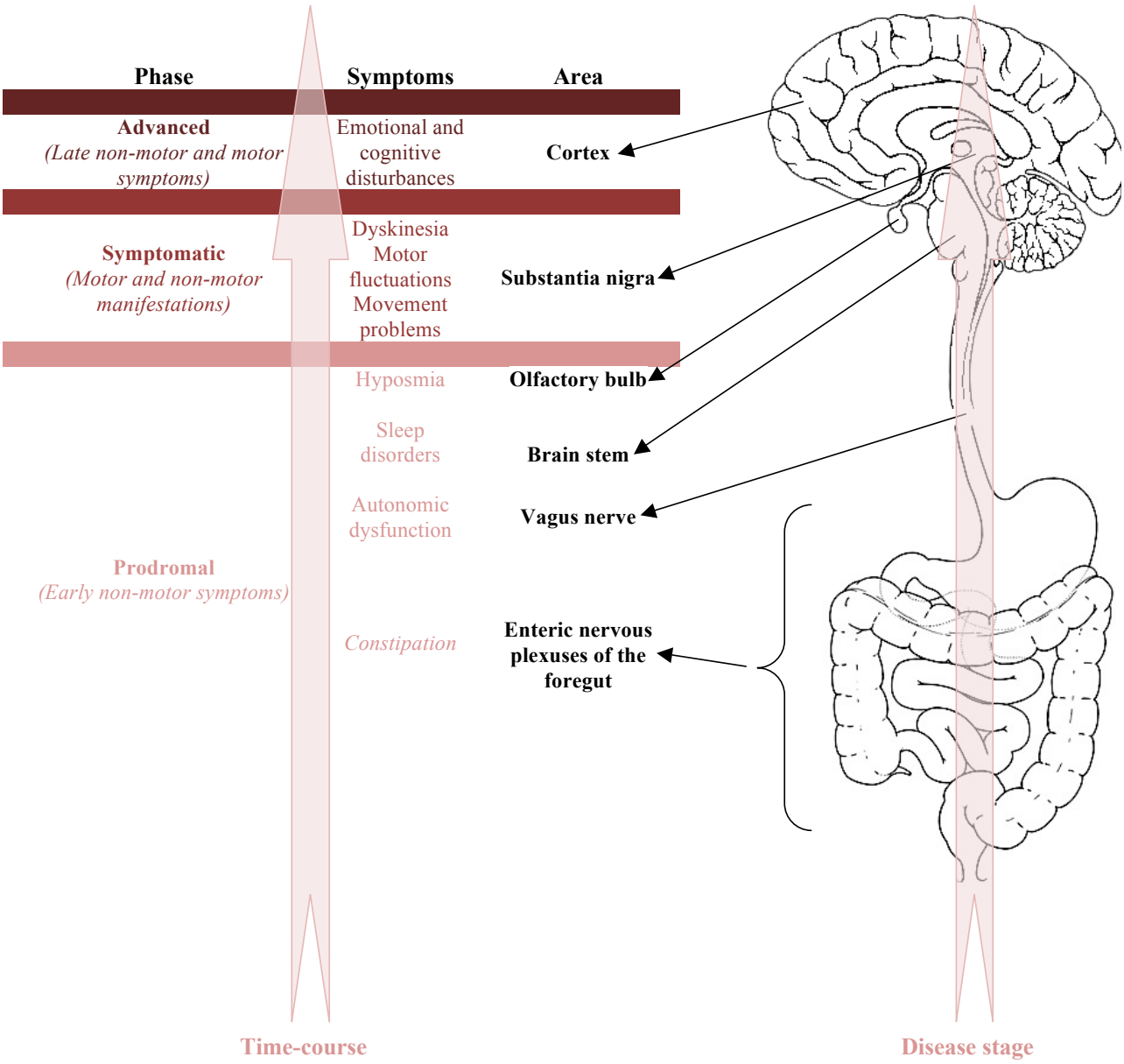


Figure 1. *Schematic illustration of the time-course and stages of Parkinson's disease based on the Braak theory*

1.1.3 Symptomatology

Regarding the multisystem nature of PD, a broad list of various symptoms could be presented, which are generally divided into two large categories: motor and non-motor symptoms. A brief classification of these symptoms can be presented as [1, 4, 16]:

- Motor symptoms
    - cardinal motor features
    - other motor features

    - drug-induced motor complications

- Non-motor symptoms
    - pre-motor (prodromal) manifestations
    - early/middle stage non-motor manifestations
    - drug-induced non-motor side-effects
    - late/advanced stage non-motor manifestations

A more specific list of the symptoms is shown in *Table 1*.

NMS are quite diverse in PD both in their presentation and timing. Although some particular symptoms are believed to occur during the long pre-motor prodromal period particularly impairment of olfaction, vagal dysfunction, constipation, and sleep disorders, they can also be observed during the early- and even the late-stage of the disease with different severities [16]. Dementia and psychosis are more likely to develop in later stages of PD, however, accumulating recent evidence suggests that mild cognitive impairment (MCI) and mood disorders could be found quite early in PD course as well [19]. Similarly, while fatigue and pain mainly dominate the clinical picture of PD during the advanced stages, they have been listed as prodromal NMS, too [4]. Nonetheless, there are some overall classifications as presented in *Table 1*.

1.1.4 Prognosis and treatment

PD is not a life-threatening disease by itself, but through some advanced complications such as serious falling, aspirations, deep vein thrombosis and pulmonary embolism in immobile late-stage patients. However, as a progressive neurodegeneration both motor and non-motor problems worsen throughout the course of the disease quite diversely. Disease progression varies largely from one patient to another and some dominant features have been shown to predict more rapid progression particularly MCI, orthostatic hypotension (OH) and REM sleep behavior disorder (RBD) [19]. A reduced death age has been shown in PD patients especially for the young-onset group [20]. However, in case of timely diagnosis and appropriate management, PD patients are expected to experience often about the same life expectancy as for the general population particularly among those who do not develop dementia [21].

Exogenous supply of brain's dopamine is the mainstay of PD medication, which has dramatically improved the management and control of movement problems. Levodopa in combination with carbidopa or benserazide, and dopamine agonists such as pramipexole, ropinirole, rotigotine and apomorphine are quite widely used to control motor symptoms.

Table 1. *Symptomatology of Parkinson's disease*

Type	Classification	Symptoms/Signs
Motor	Cardinal motor features	▪ Bradykinesia ▪ Resting tremor ▪ Rigidity ▪ Postural instability
	Other motor features	▪ Gait disturbances (shuffling gait, turning "en bloc") ▪ Decreased arm-swing ▪ Micrographia (smaller hand-writing) ▪ Camptocormia (stooped posture) ▪ Festination ▪ Freezing of gait ▪ Falling ▪ Dystonia ▪ Scoliosis ▪ Hypomimia (masked face) ▪ Hypophonia (soft speech) ▪ Drooling ▪ Dysphagia (impaired swallowing) ▪ Dysarthria ▪ Difficulty rolling in bed ▪ Difficulty rising from a chair ▪ Impaired motor coordination ▪ Akathisia (unpleasant desire to move) ▪ Restless legs ▪ Reemergence of primitive reflexes ▪ Glabellar reflex
	Drug-induced motor complications	▪ Dyskinesia ▪ Motor fluctuations (wearing-off)
Non-motor	Pre-motor (prodromal) manifestations	▪ Hyposmia (decreased sense of smelling) ▪ Rapid eye movement sleep behavior disorder (RBD) ▪ Constipation ▪ Depression ▪ Anxiety ▪ Excessive daytime sleepiness ▪ Fatigue ▪ Pain ▪ Erectile dysfunction
	Early/middle stage non-motor manifestations	▪ Mild cognitive impairment (MCI) (executive dysfunction, slowed cognitive speed, memory problems, problems in verbal fluency, difficulties in visuospatial skills) ▪ Color vision impairment and other neuro-ophthalmological disorders (blurred vision, diplopia, decreased eye convergence, etc.) ▪ Hyposmia (decreased or loss of sense of smelling) ▪ Impaired proprioception ▪ Paresthesias ▪ Depression ▪ Anxiety ▪ Apathy ▪ Autonomic dysfunction [i.e. orthostatic hypotension (OH), supine hypertension, sexual disorder, oily skin, urinary incontinence, excessive sweating]

		▪ Constipation ▪ Sleep disorders (RBD, insomnia, daytime somnolence)
	Drug-induced non-motor side-effects	▪ Impulse control disorders (ICD) (gambling, punding, compulsive buying, sexual behavior, and/or eating) ▪ Hallucination ▪ Dopamine agonist withdrawal syndrome ▪ Parkinson's hyperpyrexia syndrome (thermoregulatory failure, delirium)
	Late/advanced stage non-motor manifestations	▪ Pain ▪ Fatigue ▪ Depression ▪ Autonomic dysfunction [i.e. orthostatic hypotension (OH), supine hypertension, sexual disorder, oily skin, urinary incontinence, excessive sweating] ▪ Sleep disorders (RBD, insomnia, daytime sleepiness) ▪ Dementia

Recently, duodopa extended-released gel has been approved for continuous intestinal administration of levodopa. MAO-B inhibitors namely selegiline and rasagiline and catechol o-methyltransferase (COMT) inhibitors such as entacapone are also helpful through the inhibition of the breakdown of dopamine. Other treatment options include anticholinergics, amantadine, and deep brain stimulation (DBS) as a surgical intervention in eligible patients [22]. Management of NMS is also crucial due to their high prevalence, huge burden and considerable effects on life quality in PD patients. There are several treatment options to handle NMS that are decided individually with respect to the types and severity of each NMS that a single patient might suffer from. Level I evidence is available to treat NMS in PD only for few of them including paroxetine and venlafaxine for depression [23], and modafinil for improving patients' perception of wakefulness in daytime somnolence [24]. Other pharmacological recommendations include sildenafil citrate for erectile dysfunction, fludrocortisone for OH, cholinesterase inhibitors and memantine for dementia, methylphenidate for fatigue, oxycodone with naloxone for pain, clonazepam, melatonin and pramipexole for RBD, just to name a few [4]. Other than medications, a multidisciplinary team support consisting of a movement disorder specialist, geriatrician, specialist nurse, speech therapist, physiotherapist, occupational therapist and neuropsychiatrist is needed to efficiently tackle with a multisystem and multiorgan disease such as PD. In addition, appropriate timely palliative care is beneficial throughout the whole PD course particularly during the advanced stage of the disease [25-26].

1.2 Epidemiology of parkinsonism and Parkinson's disease

Findings from literature review on the prevalence of parkinsonism and PD are summarized in *Table 2*, which clearly shows that the rates vary widely between different ethnic groups and countries categorized according to the six World Health Organization (WHO) regions.

1.2.1 Prevalence of parkinsonism

In one survey from the *Aeolian Archipelago* in Sicily, Italy, a prevalence rate of 323.4/100,000 has been found for all types of parkinsonism in individuals aged 40 years and over [27]. In a record-based study conducted in north of Wales, United Kingdom, prevalence of parkinsonism has been reported as 122/100,000 [28]. In another study on Egyptian population aged >40 years, prevalence of parkinsonism was found to be 316.5/100,000 [29]. Other few reports resulted in a quite broad estimation for the prevalence of parkinsonism ranging from 339.6/100,000 in Columbia [30] to 659.0/100,000 in Egypt [31] and even as high as 800/100,000 in Albania [32].

1.2.2 Prevalence and incidence of Parkinson's disease

The incidence of PD rises steeply with age, from 17.4 in 100,000 person aged between 50 and 59 years to 93.1 in 100,000 person aged between 70 and 79 years, with a lifetime risk of developing the disease of 1.5% [33]. The median age of onset is 60 years and the mean duration of the disease from diagnosis to death is approximately 15 years [34]. Data on prevalence of PD is quite diverse as shown in *Table 2*. The crude prevalence rate has been estimated as low as 15 per 100,000 in China [35] to even as high as 850 per 100,000 in Caucasians [36]. In general, PD prevalence and incidence has been found to be lower in Afro-Americans, Japanese, and some other Asian countries [37]. In the Eastern Mediterranean region, data on PD prevalence is available from Egypt, Tunisia, Jordan and Saudi Arabia showing an estimated rate of 213.1/100,000 [29], 216.0/100,000 [38], 58.8/100,000 [39] and 27.0/100,000 [40], respectively.

1.2.3 Methodological issues

Besides ethnical and environmental factors that contribute in the variation of PD prevalence across countries, methodological aspects of the surveys and data collections play an important role. More specifically, one must consider sampling method, source of data collection and standardization method that have been used on the crude prevalence rates for between-countries comparisons of neuroepidemiologic data. While in developed countries prevalence data could be easily obtained through electronic patients' registries or drug tracing through the pharmacies, community-based door-to-door surveys are the most valid method of data collection in poor-resource developing countries. In a systematic review on studies published during 1965-2008 in Asian countries, the standardized prevalence of PD was shown to vary from 51.3 to 176.9/100,000 in community-based door-to-door surveys, while in record-based studies from the same geographical region the rate has been estimated to be generally lower ranging from 35.8 to 68.3/100,000 [41]. Population-based surveys such as door-to-door studies tend to overestimate PD prevalence through the ascertainment of undiagnosed cases some of which might be falsely screened, whereas record-based reports represent only diagnosed patients and definitely underestimate the real prevalence rates [42]. Yet, among population-based studies prevalence of PD is commonly higher in European and Eastern Mediterranean regions compared to the African and Eastern Asian countries (*Table 2*).

Table 2. *Prevalence rate of Parkinson disease and/or parkinsonism using different data-collection and standardization methods in different countries from each of the six World Health Organization regions*

Country	Continent	WHO Region	Condition	Data Collection Method	Standardization Method	Prevalence (/100,000)	Year
Alaska	North America	Region of the Americas	Parkinson's disease	Record-Based	Global Standardized	355.7	2009
Canada	North America	Region of the Americas	Parkinson's disease	Record-Based	Local Standardized	144.0	2003
USA	North America	Region of the Americas	Parkinson's disease	Record-Based	Local Standardized	107.0	1993
USA	North America	Region of the Americas	Parkinson's disease	Record-Based	Global Standardized	81.0	1995
USA	North America	Region of the Americas	Parkinson's disease	Capture-recapture	Local Standardized	329.3	2000
Argentina	Central/South America	Region of the Americas	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	174.3	1997
Bolivia	Central/South America	Region of the Americas	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	106.5	2003
Brazil	Central/South America	Region of the Americas	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	297.7	2006
Colombia	Central/South America	Region of the Americas	Parkinson's disease	Population-Based (door-to-door)	No Standardization	470.0	1997
Colombia	Central/South America	Region of the Americas	Parkinsonism	Capture-recapture	No Standardization	339.6	2004
Colombia	Central/South America	Region of the Americas	Parkinson's disease	Capture-recapture	No Standardization	176.4	2004
Cuba	Central/South America	Region of the Americas	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	135.0	1997
Mexico	Central/South America	Region of the Americas	Parkinson's disease	-	Local Standardized	170.0	2008
Albania	Europe	European Region	Parkinsonism	Population-Based (door-to-door)	Local Standardized	800.0	2012
Bulgaria	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	141.1	2001
Denmark	Europe	European Region	Parkinson's disease	Record-Based	Local Standardized	183.3	1997
England	Europe	European Region	Parkinson's disease	Record-Based	Local Standardized	112.5	1961
England	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	108.4	1982
England	Europe	European Region	Parkinson's disease	Record-Based	Global	70.9	1985

					Standardized		
England	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	121.0	1992
England	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	73.5	1995
England	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	91.7	2000
England	Europe	European Region	Parkinson's disease	Record-Based	Local Standardized	142.0	2010
Estonia	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	111.3	2002
France	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	320.0	1987
France	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	101.0	1994
France	Europe	European Region	Parkinson's disease	Record-Based	Local Standardized	121.0	1994
Germany	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	183.0	1987
Germany	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	713.0	1992
Italy	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	61.4	1980
Italy	Europe	European Region	Parkinson's disease	Record-Based	Local Standardized	152.3	1986
Italy	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	100.4	1987
Italy	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	95.5	1991
Italy	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	173.8	1992
Italy	Europe	European Region	Parkinsonism	Record-Based	Local Standardized	156.3	2001
Italy	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	89.7	2005
Italy	Europe	European Region	Parkinsonism	Population-Based (door-to-door)	Local Standardized	323.4	2008
Italy	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	215.6	2008
Netherlands	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	216.0	1995
Norway	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	102.4	1995

Portugal	Europe	European Region	Parkinson's disease	Record-Based	Local Standardized	130.0	1992
Russia	Europe	European Region	Parkinson's disease	Record-Based	Local Standardized	76.5	2009
Russia	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	129.0	2011
Scotland	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	91.4	1986
Spain	Europe	European Region	Parkinson's disease	Record-Based	Local Standardized	161.5	1994
Spain	Europe	European Region	Parkinson's disease	Record-Based	Local Standardized	220.6	1995
Spain	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	93.8	1999
Spain	Europe	European Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	117.6	2003
Sweden	Europe	European Region	Parkinson's disease	Record-Based	Global Standardized	76.0	1996
Ukraine	Europe	European Region	Parkinson's disease	Record-Based	Local Standardized	61.4	2013
Egypt	Middle East	Eastern Mediterranean Region	Parkinsonism	Population-Based (door-to-door)	Local Standardized	316.5	2009
Egypt	Middle East	Eastern Mediterranean Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	213.1	2010
Egypt	Middle East	Eastern Mediterranean Region	Parkinson's disease	Population-Based (door-to-door)	No Standardization	452.1	2012
Egypt	Middle East	Eastern Mediterranean Region	Parkinsonism	Population-Based (door-to-door)	No Standardization	659.0	2012
Iran	Middle East	Eastern Mediterranean Region	Parkinsonism	Population-Based (door-to-door)	Global Standardized	**284.9**	**2012**
Iran	Middle East	Eastern Mediterranean Region	Parkinsonism	Population-Based (door-to-door)	Local Standardized	**222.9**	**2012**
Iran	Middle East	Eastern Mediterranean Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	**182.3**	**2012**
Iran	Middle East	Eastern Mediterranean Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	**142.7**	**2012**
Israel	Middle East	European Region	Parkinson's disease	Population-Based	No Standardization	240.0	2002

				(door-to-door)			
Israel (Arab population)	Middle East	European Region	Parkinson's disease	Record-Based (drug-tracer)	Local Standardized	43.2	2010
Jordan	Middle East	Eastern Mediterranean Region	Parkinson's disease	Record-Based	No Standardization	58.8	2009
Saudi Arabia	Middle East	Eastern Mediterranean Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	27.0	1993
Tunisia	Middle East	Eastern Mediterranean Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	216.0	
Turkey	Middle East	European Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	202.0	2011
China	Asia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	51.3	1985
China	Asia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	16.7	1991
China	Asia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	112.2	1996
China	Asia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	109.3	2003
China	Asia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	112.2	2005
China	Asia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	176.9	2005
India	Asia	South-East Asia Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	140.6	1993
India	Asia	South-East Asia Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	76.0	2004
Japan	Asia	Western Pacific Region	Parkinson's disease	Record-Based	Global Standardized	68.3	1983
Japan	Asia	Western Pacific Region	Parkinson's disease	Record-Based	Global Standardized	57.9	1990
Japan	Asia	Western Pacific Region	Parkinson's disease	Record-Based	Global Standardized	68.2	1996
Japan	Asia	Western Pacific Region	Parkinson's disease	Record-Based	Global Standardized	61.4	1996
Japan	Asia	Western Pacific Region	Parkinson's disease	Record-Based	Global Standardized	35.8	2002

Korea	Asia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	No Standardization	374.0	2007
Singapore	Asia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	61.9	2004
Taiwan	Asia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	113.1	2001
Thailand	Asia	South-East Asia Region	Parkinson's disease	Record-Based	No Standardization	424.6	2011
Libya	Africa	Eastern Mediterranean Region	Parkinson's disease	Record-Based	Local Standardized	60.0	2007
Nigeria	Africa	African Region	Parkinson's disease	Population-Based (door-to-door)	Local Standardized	10.0	1987
Tanzania	Africa	African Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	40.0	2008
Australia	Australia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	Global Standardized	439.4	2005
Australia	Australia	Western Pacific Region	Parkinson's disease	Population-Based (door-to-door)	No Standardization	146.0	2006
Australia	Australia	Western Pacific Region	Parkinson's disease	Record-Based	Global Standardized	71.3	2007
New Zealand	Australia	Western Pacific Region	Parkinson's disease	Record-Based	Global Standardized	76.0	1992

Findings from the current PhD project are highlighted in grey.

As it is shown in *Table 2*, different methods of standardization have been applied to adjust crude data on PD prevalence including either a global reference (i.e. WHO, USA or Europe standard reference populations), or national/regional references. Using a global hypothetical standard population has made it possible to fairly compare prevalence rate of PD between different countries with various national population pyramids with their own specific age and sex distribution [42]. Among the globally standardized rates, the lowest and highest prevalence of PD has been reported from China (16.7/100,000) [35] and Australia (439.4/100,000) [43], respectively (*Table 2*). Throughout the studies that have reported only national standardized rates, PD prevalence ranges from 10.0/100,000 in all age groups in Nigeria [44] to 713.0/100,000 among the population older than 65 years in Germany [45] (*Table 2*).

1.2.4 Importance and knowledge gap

Iran is the world's 17th most populous country with 78.4 million inhabitants [46], which is aging rapidly. This demographic shift has caused tremendous concerns for the future healthcare of Iranian population. According to the national census in Iran, the population aged 60 and older constituted 6.6% of the whole population (71 million) in 2006, which accounts for more than four million individuals [47]. Recently, the proportion of those with ≥60 *yrs* of age has increased 1% from 2006 to 2011 [48-49] and is estimated to reach 10.5% in 2025 and as high as 21.7% in 2050 [49-50]. This trend will lead to a rise in the incidence of neurodegenerative diseases including PD in near future, which implies a major health problem with its consequences to both healthcare system and society. There are a number of epidemiological studies from different developed countries as listed in *Table 2* that provides useful knowledge and important information concerning the epidemiological and clinical aspects of PD, but little attention has been focused in Iran on the neuroepidemiology of PD. Moreover, data on the prevalence rate of PD in other countries could not be cited in other societies due to different ethnic groups and environments even from the neighboring countries. Therefore, it was necessary to perform a neuroepidemiologic study in Iranian population to achieve relevant data on PD prevalence.

1.3 Nutritional status in parkinsonian patients

1.3.1 Prevalence of malnutrition

As a general aspect of daily life, nutritional status plays a crucial role in everyday's well-being especially in patients suffering from a chronic condition such as PD [51-52]. Several symptoms potentially affect nutrition in PD patients including difficulty swallowing and chewing, drooling, dysphasia, motor problems in cutting and transporting the foods, constipation and even psychological disorders such as depression, which are associated with reduced food

intake and changes in dietary habits [53-56]. Dysphagia accompanies with difficulties in the intake of both solid and liquid foods in up to 50-70% of PD patients [57]. All these symptoms increase the risk of nutritional insufficiency in individuals with PD leading to a higher burden of disease, lower quality of life (QoL) and consequently increasing morbidity and mortality [55, 58]. One systematic review showed that the prevalence rate of malnutrition in PD varied between 0% and 24% in different studies, while 3–60% of them were at risk of malnutrition [59]. This wide range of estimations is largely attributed to different assessment methods applied for nutritional status in PD population [55, 59]. Two studies have estimated that 20-23% of PD patients are at risk of malnutrition based on validated instruments such as the Mini Nutritional Assessment (MNA) [60-61]. Other investigations have mainly used anthropometric measurements such as body mass index (BMI) and weight showing different results.

1.3.2 Risk factors of malnutrition

On one hand, different motor and non-motor conditions, pharmacological treatment and side-effects can influence nutritional status in PD patients [62-63]. On the other hand, malnutrition can also worsen the symptoms and different aspects of QoL such that improvement of nutritional status has been recently shown to improve QoL in PD patients [64]. *Table 3* summarizes the findings of investigations on the risk factors of nutritional insufficiency in PD patients. Several outcome measures have been evaluated including different anthropometric indices and various nutritional assessment tools in each of the previous studies. However, severity of motor symptoms [65-69], motor complications [70], psychiatric disorders [60, 67, 69], disease duration [61], sex [66, 71] and age [66, 69], cognitive function [66-67], sleep disorder [60], gastrointestinal symptoms [60, 72] and medication [68-69] have been found to affect nutritional status in PD patients.

1.3.3 Importance and knowledge gap

Despite the hypothetical strong connection between PD and nutrition, prevalence of malnutrition and investigation of its determinants have been usually ignored. Few studies have estimated the magnitude of nutritional insufficiency in PD most of which have used weight, BMI and other anthropometric measurements as the main indicator. Lack of a matched control group from the same community as the patients is another methodological problem that affects the validity of interpretations [59]. Furthermore, even fewer studies have focused on a broader picture of nutritional status using validated instruments [*i.e.* MNA, Subjective Global Assessment (SGA)] other than just anthropometric indices in PD patients. Even though a couple of reports did use the MNA, still there is not enough evidence on the relationships between different features of PD, consisting of both motor and non-motor, and nutritional status as well as the counterfactual effects of malnutrition on QoL in PD patients.

Table 3. *Literature review on the list of determinant/risk factors for nutritional insufficiency in Parkinson's disease patients*

Study	Year	Design	Country	Sample Size	Disease Stage (H & Y)	Outcome	Determinant Factors
Durrieu et al [71]	1992	Cross-sectional	France	65	2.4 (mean)	Weight, CC Protein biomarkers	Female sex
Markus et al [70]	1993	Cross-sectional	United Kingdom	95	3 (mean)	Weight, BMI, MAC, skin-fold thicknesses	Dyskinesia
Beyer et al [65]	1995	Longitudinal comparison with control group	USA	51	2 (median)	Weight, BMI, MAC, skin-fold thicknesses	H & Y stage
Lorefalt et al [66]	2004	Longitudinal comparison with control group	Sweden	26	-	Weight, BMI, body fat mass, resting energy expenditure, energy intake	Rigidity, Tremor, cognitive function, female sex, age, low physical activity
Uc et al [67]	2006	Longitudinal comparison with control group	USA	49	2.1 (mean at the middle of study)	Weight	H & Y stage, emergence of visual hallucinations, dementia
Barichella et al [61]	2008	Longitudinal comparison	Italy	61	-	MNA score, weight, BMI	Disease duration
Wang et al [60]	2010	Cross-sectional	China	117	2 (median)	MNA score	Constipation, vomiting, loss of interest, inability to concentrate, depression, sleep quality, anxiety
Barichella et al [68]	2013	Cross-sectional	Italy	208	2 (median)	MUST score, weight, BMI, MAC, skin-fold thicknesses	Number of dysautonomia symptoms, H & Y stage, levodopa dose
Sheard et al [69, 72]	2013	Cross-sectional	Australia	125	2 (median)	SGA, weight, BMI, MAC, WC	Loss of appetite, constipation, early satiety,

							problems in swallowing, UPDRS-Part II, UPDRS-Part III, weight-adjusted daily levodopa dosage, age at diagnosis, anxiety, depression, living alone
Fereshtehnejad et al [73]	2014	Cross-sectional	Iran	150	2 (median)	MNA score, weight, BMI, MAC, CC,	Total UPDRS, disease duration, female sex, weight-adjusted daily levodopa dosage, H & Y stage, anxiety, depression, fatigue

H & Y: Hoehn and Yahr stage; MNA: mini nutritional assessment; SGA: subjective global assessment; BMI: body mass index; CC: calf circumference; MAC: mid-arm circumference; WC: waist circumference; MUST: malnutrition universal screening tool
Findings from the current PhD project are highlighted in grey.

1.4 Quality of life in parkinsonian patients

1.4.1 Determinants and correlates

Health-related quality of life (HRQoL) is a major indicator for health outcome assessment in PD researches [74]. As a valid multi-dimensional index, HRQoL refers to the health aspects of daily life's quality regarding physical health, emotional status and cognition [75]. With respect to the multisystem and chronic progressive nature of PD, it is of utmost importance to investigate the factors affecting HRQoL in people with PD. Patients with PD experience a wide range of motor and non-motor symptoms, each of which potentially affects different aspects of HRQoL including daily physical activity, as well as emotional and cognitive tasks. In spite of the growing number of studies on HRQoL in PD patients from different countries, it remains unclear which demographic and clinical factors are the key predictors of HRQoL [76]. While more attentions were conventionally paid to the cardinal motor features of PD, there is rapid increasing evidence showing the immense burden of NMSs on the lives of the people with PD [4]. It has been demonstrated from some previous studies that NMSs have a larger impact on patients' HRQoL than motor symptoms [77-78]. Results from a recent systematic review concluded that depression, disease severity and disability, motor features such as gait impairments and complications of therapy were the major predictors of poor HRQoL in PD patients [76].

1.4.2 Importance and knowledge gap

Knowledge on the determinants of HRQoL in PD assists clinicians to target their examinations and treatment strategies in order to diminish the functional and emotional burden of PD [76]. Many studies have investigated the impact of different variables on HRQoL in PD patients including disease severity, motor and non-motor symptoms, nutritional status, demographic and socioeconomic characteristics [64, 73-74, 76, 79-83]. Thus far, a few of them have included the broad range of parkinsonian features all together, assess the interactions between different symptoms and the mediation pathways, and compare their independent role and strength of their effect on HRQoL. On the other hand, patients with PD show significant heterogeneity in their motor and non-motor features [84], which is a great obstacle in generalisability of the pattern and determinants of HRQoL for PD patients with different phenotypes.

1.5 Heterogeneity in Parkinson's disease

It is now already known that no two PD patients are alike in clinical manifestations, response to treatment, overall prognosis, and many other aspects of PD. This heterogeneity makes PD an inappropriate disease to have a "*one size fits all*" caring approach [25, 85]. Diverse clinical

phenotypes of PD patients have recently highlighted the concept of heterogeneity and the need for identification of subtypes in PD. Defining different PD phenotypes and further clarification of their differences is crucial for a better understanding of underlying disease mechanisms and genetic features, prediction of disease course, and eventually perhaps more efficiently-designed personalized management strategies [19].

1.5.1 Importance and knowledge gap

The National Institute of Health has recently delineated subtype-identification as one of the top priorities in the field of PD clinical research [86]. While different research groups are now working on definition of distinct PD phenotypes, there is also a dearth of information about the heterogeneity in pattern and determinants of HRQoL between different PD subtypes.

2 AIMS

2.1 General aims

Regarding the previously mentioned knowledge gap, the general goal of this project was to investigate neuroepidemiologic features of PD in Iran, focusing on screening and prevalence of parkinsonism, nutritional status, clinical and psychiatric features and quality of life. For this purpose, we also needed to validate several questionnaires and make a new screening instrument.

2.2 Specific aims

- *Study I*: This study had two objectives as follows:
    - to assess the validity and reliability of the Persian version of the short-form 8-item Parkinson's Disease Questionnaire (PDQ-8)
    - to compare psychometric properties of the short- versus long-form versions of the PDQ to evaluate HRQoL in PD patients
- *Study II*: This study had two objectives as follows:
    - to devise and validate a sensitive and specific screening questionnaire for parkinsonism based on different symptoms of PD
    - to compare diagnostic value of our newly composed questionnaire with the previously developed screening instruments for parkinsonism
- *Study III*: to estimate the prevalence rate of probable parkinsonism in the huge urban area of Tehran, Iran following a community-based door-to-door survey
- *Study IV*: to estimate the prevalence of individuals with malnutrition or at risk of malnutrition in a community of Iranian PD patients and compare it with a matched control group using anthropometric measurements and MNA
- *Study V*: This study had two objectives as follows:
    - to investigate the association between motor, psychiatric and fatigue features with nutritional status in PD patients using anthropometric measurements and MNA

- to evaluate the effects of nutritional insufficiency on different domains of HRQoL in people with PD

- *Study VI*: This study had four objectives as follows:
  - to identify the factors that affect HRQoL in Iranian PD patients
  - to compare the independence and strength of their effects on HRQoL
  - to investigate the general pattern of HRQoL with the best hypothesized structural model
  - to explore the structural heterogeneity in the optimum model for HRQoL between different PD phenotypes

3 METHODS

In the whole PhD project, data were collected through several settings as described here:

3.1 Movement Disorder Clinic

3.1.1 Setting and study population

In *study I*, *study II*, *study IV*, *study V* and *study VI*, the entire or at least part of the data were collected from a referral Movement Disorders Clinic in Tehran, Iran. In this cross-sectional project a total number of 157 Iranian patients with IPD were consecutively recruited from this outpatient clinic during October 2011 and December 2012.

3.1.2 Eligibility

In *study I*, *study IV*, *study V* and *study VI*, patients were eligible for recruitment if they fulfilled the following inclusion criteria at the time of initial assessment:

- Diagnosis of IPD based on the *United Kingdom Brain Bank* criteria [2]
- Age ≥30 *yrs*

Patients with any of the following characteristics were all excluded from the above-mentioned studies:

- Cognitively unable to answer valid responses or moderate to severe dementia [mini-mental state examination (MMSE)<24] [87]
- Other types of parkinsonism such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and vascular or drug-induced Parkinsonism
- Dystonia
- Essential tremor

In *study II*, patients with atypical parkinsonism (n=10), dystonia (n=14) or essential tremor (n=7) were also enrolled in the study to compare the diagnostic value of screening questionnaires for different discriminative purposes as described [88]. Of note, the same neurologist specialized in movement disorders evaluated all participants for eligibility.

In *study IV* and in addition to the above-mentioned criteria, patients with other chronic comorbidities influencing nutritional state such as hypertension and diabetes mellitus and those

who were following special diets were also excluded since the main aim of this sub-study was to compare nutritional status between PD patients and healthy controls [55].

3.1.3 Subgroups

In *study VI*, IPD patients were divided into several subgroups regarding their onset-age, progression rate and dominant symptom as follows:

- Onset-age: younger-onset (n=50, diagnostic age ≤50 *yrs*) versus older-onset (n=106, diagnostic age >50 *yrs*)
- Progression: slow (n=95) versus rapid (n=40) based on the clustering solution recommended by *Gasparoli et al* [89]
- Dominant symptom: tremor (n=76) versus non-tremor (n=75) based on the median value of the tremor motor score

3.1.4 Data collection

In the outpatient clinic, data collection was performed through face-to-face interviews with eligible patients and if necessary their caregivers by a trained group of medical interns and general physicians to fill in validated questionnaires and scales. As for diagnosis, all clinical examinations were done by the same movement disorders specialist for all patients. Medical records and documents were also used to collect some baseline information. All assessments were performed when the patients were in the "on" status.

3.1.5 Variables

In this phase of our project, the following variables and characteristics were recorded:

- Demographic and baseline data:
  - age
  - sex
  - educational status
  - co-morbidities (type and total number)
  - duration of PD (time passed from diagnosis)
  - history of levodopa administration
- Motor severity:

- Unified Parkinson's Disease Rating Scale (UPDRS) subscales I–IV, 1987 version [90]
- Hoehn and Yahr (H & Y) staging
- Schwab and England activities of daily living (ADL)
- motor impairment score [91]: score "*A*" as sum of UPDRS-Part III items on facial expression, tremor, rigidity, and bradykinesia (considered relatively dopamine-responsive) and score "*B*" as sum of UPDRS-Part III items concerning speech and axial impairment (considered relatively levodopa non-responsive)
- dyskinesia score: sum of UPDRS-Part IV items 32-34
- fluctuation score: sum of UPDRS-Part IV items 36-39

- Motor subtypes:
  - postural-instability-gait-difficulty (PIGD) score [92]: sum of UPDRS-Part III items concerning rise, gait, and postural instability
  - FOSS score [92]: sum of UPDRS-Part II items on freezing, speech and swallowing
  - predominance of core manifestations: proportion of UPDRS-Part III ''on'' motor scores accounted for tremor (items 20–21), rigidity (item 22), bradykinesia (items 23–26 and 31), and gait (items 27–30) in percentage
  - asymmetry Index [93]: absolute differences in UPDRS between sides divided by the total UPDRS III (0 = "*perfect symmetry*", 1 = "*absolute asymmetry*")
  - axial/limb ratio: sum of UPDRS-Part III items 18, 19, 22 and 27-30 divided by sum of UPDRS-Part III items 20-26
  - presence of falls and freezing

- Non-motor manifestations:
  - depression: evaluated by Hospital anxiety and depression scale (HADS) [94]
  - anxiety: evaluated by HADS [94]

- hallucinations/Illusions: evaluated using UPDRS-Part I, item 2
- apathy: evaluated using UPDRS-Part I, item 4
- fatigue: by means of the Fatigue Severity Scale (FSS) [95]
- psychosocial functioning: evaluated by the scales for outcomes in Parkinson's disease-psychosocial questionnaire (SCOPA-PS) [96]

- Nutritional status: using the Mini Nutritional Assessment (MNA) [97]
- Anthropometric measurements:
  - weight
  - height
  - body mass index (BMI)
  - mid arm circumference
  - calf circumference
- Health-related quality of life (HRQoL): evaluated by the Parkinson's disease questionnaire (PDQ) [98]

3.2 Control groups

For two studies, control groups were enrolled to answer the underlying research questions. In *study II*, 110 healthy individuals without any history of neurological diseases who aged ≥40 *yrs* were recruited at the same period of time as for the cases. They were selected from an outpatient ophthalmology clinic and three senior medical students performed a complete neurological examination to confirm not having any symptomatic neurological deficit. After enrollment, the same baseline checklist and screening questionnaires were filled through face-to-face interviews. In *study II*, the patients and controls were frequently matched by sex distribution and mean age [88].

In *study IV*, another control group was selected consisting of 145 sex- and age-matched healthy individuals. For this purpose, the controls were randomly recruited from the medical staff and the patients' relatives in Sina and Imam Khomeini hospitals in Tehran, Iran during the same period as for the cases in this sub-study (January 2012-September 2012). Regarding the main objective of *study IV*, the controls were selected from the same geographical region as the IPD patients in order to avoid the effect of cultural differences on nutritional habits. The similar

eligibility criteria were applied for the controls as for the case group except the patients exhibited PD symptoms. Therefore, similar to the case group, those participants under the age of 35 *yrs*, suffering from chronic conditions affecting their nutritional habits such as hypertension and diabetes, and those following special diets were excluded from the control group, too [55].

3.3 Community-based door-to-door study

3.3.1 Setting and study population

Data was collected from a different setting in *study III*. This community-based door-to-door study was performed in Tehran urban area, Iran during October 2011 and January 2012 as the prevalence date point. As the capital city of Iran, Tehran is the largest urban area in West Asia with a population of >8,300,000 inhabitants surpassing 14,000,000 in the wider metropolitan region [46] with 22 urban districts with heterogeneous population density according to the latest estimations (*Figure 2*). This study targeted adult population of Tehran urban area who aged ≥30 *yrs* at the time of assessment.

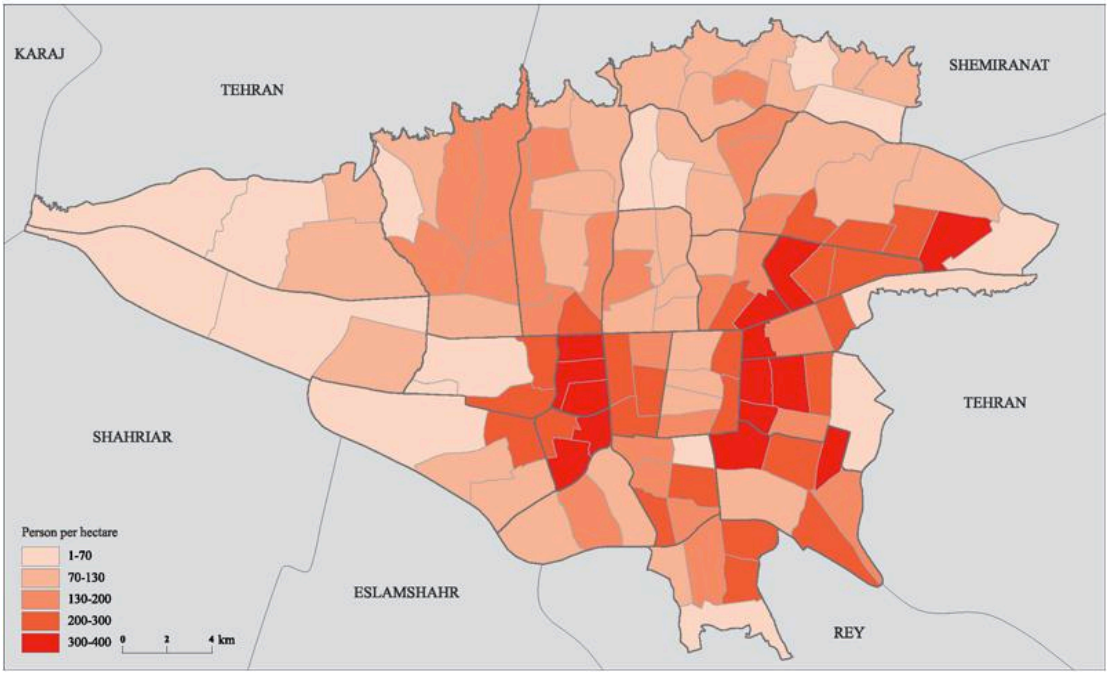


Figure 2. *Population density map of Tehran urban area in 22 districts (from: Atlas of Tehran Metropolis)*

3.3.2 Sampling method

As shown in *Figure 2*, Tehran urban area has 22 hierarchical districts regarding not only population density but also socioeconomic status. Therefore, it was crucial to perform sampling in a way to cover all regions with a representative selected population. For This reason, we used a probability multistage sampling method covering all 22 urban districts of Tehran in *study III*. Each district was considered as one sampling stratum where each of them consisted of several blocks and households as the clusters. Throughout Tehran area, there is a network of "*Health Centers*" consisting of 374 subunits covering all districts, which are organized by the health deputy of Tehran municipality. Each of the "*Health Centers*" is responsible for a determined number of residing blocks and households that are coded by unique numbers. Following stratification, we used cluster sampling to randomly select the needed number of households within the coverage zone of each "*Health Centre*" to fulfill the calculated proportional sample size for each subunit in every district. This procedure was performed for each district and subunit resulting in representative selected households.

3.3.3 Data collection

In *study III*, data collection was performed through face-to-face interviews with the inhabitants of selected households. In September 2011, a one-day workshop was held to train the surveyors who were mostly healthcare workers employed by the "*Health Centers*" of each district. Each of the surveyors was responsible for a determined number of households within their affiliated subunit and district. All members of each selected household were asked to participate in the survey if they aged ≥30 *yrs* and agreed to contribute after necessary information about the survey and study aims was given. After agreement, study checklist was filled through face-to-face interview by the surveyor, which consisted of three main sections including demographic information (i.e. age, sex, educational level, marriage and working status), comorbidity profile and screening questions. In *study III*, we used the screening questionnaire for parkinsonism validated in *study II* [88]. In overall 20,621 individuals answered study checklist including baseline variables and screening questionnaire. Nevertheless, information from 19,500 persons were entered in the final analysis regarding missing values and data cleaning, which showed 94.6% rate of valid participation.

3.4 Instruments, questionnaires and measurements

3.4.1 Screening questionnaire

To make the new screening tool in *study II*, we evaluated all of the symptoms previously included in questionnaires for screening of PD. Following thorough literature review, the questions that require no physical examination and were the best representative for each PD symptom were selected. This comprehensive list was actually constructed by combining the

items from previously validated questionnaires used for screening of PD including the screening instrument of the Sicilian neuro-epidemiology study (SNES) [99], the Baylor Health Screening Questionnaire (BHSQ) [100], telephone questionnaire for Parkinson's disease [101], original and modified WHO screening instruments to measure the prevalence of neurological disability in resource-poor settings [102-103] and the questionnaires either developed or modified by *Tanner* [104], *Daurate* [105], *Chan* [106], *Setthawatcharawanich* [107] and *Sevillano* [108]. A bilingual person translated all of these questions into Persian language and wording was trans-culturally approved by the experts for face validity. Of note, some general questions on non-PD specific neurologic symptoms from the SNES questionnaire [99] were kept in the merged instrument to check the validity of the answers from the patients. The new comprehensive preliminary questionnaire consisted of 25 unique items (*Table 9*) on different neurological symptoms. *Appendix 1* shows all questions that were used in this screening instrument and the ones that were finally selected. In order to prevent information bias, surveyors thoroughly explained technical terms and symptoms for all subjects including those controls who might not be familiar with the symptoms and/or have lower level of education.

3.4.2 Fatigue severity scale (FSS)

The FSS is an easy-administered tool to evaluate fatigue in a variety of medical and neurologic disorders. The scale assesses relationship between fatigue intensity and functional disability. It consists of nine questions with a seven-point Likert scale from 1 to 7, stating "*strong disagreement*" to "*strong agreement*". Each patient is asked to rate the level of fatigue during the previous week and a total average score ranging from 0 to 7 where higher scores correspond to more severe fatigue is calculated for each patient [95]. The FSS was previously translated into Persian language and has been found to be valid and reliable in patients with multiple sclerosis [109]. During the validation phase of this project, we evaluated psychometric properties of the Persian-translated version of the FSS in Iranian patients with IPD [110].

3.4.3 Hospital anxiety and depression scale (HADS)

The HADS is a self-assessment screening tool that was designed to determine levels of anxiety and depression in a non-psychiatric population attending medical clinics. It has 14 questions in two sections: seven questions are related to depression and the other seven focus on anxiety. Each question is scored from 0-3, where 0 = "*not at all*", and 3 = "*very often indeed*", therefore, each section is worth 0–21 points by adding up the answers for all items that provides separate scores for either depression or anxiety where in both sub-scales, a higher score shows more severe condition [94]. The Persian-version of the HADS questionnaire has been previously shown to have a Cronbach's alpha coefficient of 0.78 for anxiety and 0.86 for depression [111].

3.4.4 Scales for outcomes in Parkinson's disease-psychosocial questionnaire (SCOPA-PS)

The SCOPA-PS questionnaire is a self-administered 11-item scale assessing severity of psychosocial functioning during the last month. Items are scored with a four-point Likert scale ranging from 0 = "*not at all*" to 3 = "*very much*". By adding up the scores of the individual items, the sum score is calculated, which is then transformed into percentage values. This summary index ranges from 0 to 100% such that the higher scores indicate worse psychosocial functioning [96]. During the validation phase of our project, three native Persian speakers fluent in English translated the SCOPA-PS into Persian. Later on an English-native fluent in Persian who had neither access to the original version of the questionnaire nor involved in the study back translated the SCOPA-PS into English. Wording modifications were performed following the comparison of the back-translated versus the original version of the SCOPA-PS. Finally, the confirmed joint version was named "*SCOPA-PS, Persian version*" and its psychometric properties were examined prior to be applied in the main sub-studies [112].

3.4.5 Anthropometric measurements

Anthropometric measurements consisting of mid arm circumference (MAC), calf circumference (CC), weight and height were performed by trained medical staff for all participants in *study IV*, *study V* and *study VI*. Calibrated floor scales were used to measure body weight between 3 *p.m.* and 5 *p.m.* while the subjects wore light clothing with no shoes or coats. For all patients, standing height was measured by means of a stadiometer at the head level, with the subject's bare feet close together, standing erect and looking straight ahead. No height adjustment was needed since there was no case of considerable stooped posture. Body mass index was calculated as body weight (*kg*) divided by the square of height (m^2). For MAC measurement, the mid-point between the acromial surface of scapula and the olecranon process of elbow was marked by the examiner on the back of the arm, while the subjects were holding their forearm in a horizontal position with their palm up. Afterwards, a flexible inextensible tape was circled around the maximum girth of the proximal part of forearm to record MAC while the subject's arm was hanging down freely along their trunk at their sides. In order to gauge CC, a flexible tape was circled around the maximal circumference between the ankle and the knee in standing position [50].

3.4.6 Mini-nutritional assessment (MNA)

As a combined screening and assessment tool, MNA is a rapid instrument to identify risk of malnutrition. The questionnaire is composed of 18 brief items divided into two sections: 6 screening questions in section I (14 points) and 12 assessment questions in section II (16 points). The items include BMI, weight loss, MAC, CC, appetite, medication, general and cognitive health, dietary matters, autonomy of feeding, self-perception of health and nutrition

and subjective judgment of malnutrition. Total score of the MNA ranges between 0 and 30 where a score of <17 indicated "*malnutrition*", scores of 17–23.5 points signified cases of being "*at risk for malnutrition*", and the scores ≥24 points indicates "*normal nutritional status*" [97]. In our project, we have used the Persian-translated version of MNA provided by *Nestlé Nutrition Institute*. Validity and reliability of this tool was checked during the validation phase of our project [113].

3.4.7 Parkinson's disease questionnaire (PDQ)

The PDQ is the most common disease-specific measure to assess health-related quality of life (HRQoL) in PD patients. In the long format of the questionnaire (PDQ-39), 39 items assess eight aspects of HRQoL in PD consisting of: mobility (10 questions), activities of daily living (ADL) (6 questions), emotional well-being (6 questions), stigma (4 questions), social support (3 questions), cognitions (4 questions), communication (3 questions) and bodily discomfort (3 questions). The questions are coded in a Likert-scale from 0 to 4, where 0 = "*never*", 1 = "*occasionally*", 2 = "*sometimes*", 3 = "*often*" and 4 = "*always*". A score ranging from 0 to 100% is calculated for each domain. The average score of all domains provides a single figure from 0 to 100%, called PD summary index (PDSI) in which zero indicates the best level of HRQoL and 100% represents the worst condition [98]. The short version of the PDQ (PDQ-8) has only eight questions consisting of one single item representing each of the HRQoL domains. In this project, we used the Persian-translated version of the PDQ-39 questionnaire, which has been previously demonstrated to have high reliability with a Cronbach's alpha coefficient of 0.93 for the total questionnaire [114]. Moreover, we extensively assessed psychometric properties of the Persian version of the PDQ-8 in *study I* [115].

3.4.8 Unified Parkinson's disease rating scale (UPDRS)

The UPDRS is an efficient tool, which is most commonly used in clinical studies of PD [116]. The scale covers different aspects of the disease such as NMS (part I), ADL (part II), motor examination (part III) and treatment complications (part IV). In our project, we have used all the subscales I – IV, 1987 version consisting of 42 items with a maximum score of 147 that indicates worst disability [90, 117]. Two other scales have been supplanted by the UPDRS namely Hoehn and Yahr Stage and Schwab and England ADL, both of which have been used in our project. The Hoehn and Yahr stage is a widely accepted staging system to describe progression of PD symptoms, which assesses daily activity limitations and the disease severity based on clinical findings and functional disability. It is expressed as a number on a scale of 0 through 5, where a higher stage represents greater levels of functional disability. In stage 0 there are no visible symptoms of PD, and in stage 5 symptoms are present on both sides of the body, indicating patients who are not able to walk [118]. The Schwab and England ADL is a

scale that estimates the ability to perform daily activities in terms of speed and independence in PD patients. A completely independent individual gets 100% score and a complete dependent individual, as seen in bed-ridden patients, gets a score of 0%. Therefore as the score increases, the level of independence is higher indicating a lower level of disability [119]. Table 4 summarizes the main characteristics of the scales and questionnaires that have been used in our project.

Table 4. *Number of items, domains, range and direction of the scores for the scales and questionnaires used in this project*

Questionnaire/Scale	Number of Items	Domains/Sections	Range of Score	Direction of Score
Unified Parkinson's Disease Rating Scale (UPDRS)	42	Part I (Mentation) (4 items) Part II (ADL) (13 items) Part III (Motor examination) (14 items) Part IV (Complications) (11 items)	0-147	Higher score ≈ Higher severity
Hospital Anxiety and Depression Score (HADS)	14	Depression (7 items) Anxiety (7 items)	0-21	Higher score≈ More severe depression/anxiety
Fatigue Severity Scale (FSS)	9	Fatigue	0-7	Higher score≈ More severe fatigue
Scales for Outcomes in Parkinson's Disease-psychosocial Questionnaire (SCOPA-PS)	11	Psychosocial functioning	0-100%	Higher score≈ Worse psychosocial functioning
Mini Nutritional Assessment (MNA)	18	Screening (6 items) Assessment (12 items)	0-30	Lower score≈ Worse nutritional status
Parkinson's Disease Questionnaire-39 items (PDQ-39)	39	Mobility (10 items) ADL (6 items) Emotional well-being (6 items) Stigma (4 items) Social support (3 items) Cognitions (4 items) Communication (3 items) Bodily discomfort (3 items)	0-100%	Higher score≈ Poorer quality of life
Parkinson's Disease Questionnaire-8 items (PDQ-8)	8	Health-related quality of life (HRQoL)	0-100%	Higher score≈ Poorer quality of life

ADL: activities of daily living

3.5 Statistical methods

3.5.1 Sample size calculations

Regarding the prevalence rate of 257/100,000 for PD patients that was estimated in a door-to-door survey in Caucasians[120], and the effect size of 7/100,000 with the assumption of 0.05 for type I (α) error in the estimation, total needed sample size was calculated as 16,000 individuals for study III, using the following formula (where *P* represents the estimated prevalence rate and *d* shows the effect size of the estimation):

$$N = \frac{Z\alpha^{2} \times P(1-P)}{d^{2}}$$

3.5.2 Description

Data were described and analyzed using IBM SPSS Statistics for Windows, version 22.0 (Armonk, NY: IBM Corp.). For description of categorical variables frequency percentage was used. For continuous variables, mean and standard deviation (SD) were reported if the normality of distribution was shown by the Kolmogorov-Smirnov test. Otherwise, median and interquartile range (IQR) was used to describe skewed numeric variables. In validation studies, minimum, maximum and coefficient of variation (CV) were also reported for each of the items of the assessed questionnaires. In order to guarantee the acceptability of a scale, floor and ceiling effects were calculated, which were considered acceptable if less than 15% [121].

3.5.3 Standardized prevalence rates

To calculate the 95% confidence intervals (CIs) for prevalence rates of parkinsonism in *study III*, standard error (SE) of estimation was calculated using following formula ("*P*" is the point prevalence rate and "*N*" is the total sample size):

$$SE = \sqrt{\frac{P(1-P)}{N}}$$

Data on the age and sex distribution of the entire Tehran population based on the latest accessible national census [46] was used to adjust crude prevalence rates. Furthermore, we used "*WHO Standard Population*" as a unique standard age- and sex-specific distribution of a hypothetical population [122] to readjust the prevalence rates with an international reference to be able to compare the prevalence rates of our study with other countries.

3.5.4 Reliability and validity

In validation studies, reliability and internal consistency of the questionnaires were examined using Spearman correlation test where the mean score of each item was correlated with the total score of each scale. Furthermore, Cronbach's alpha intraclass coefficient and its 95% confidence interval (CI) were also calculated for the entire questionnaire, within each domain if applicable and different subgroups of PD patients regarding age-group, sex, level of education and disease severity. Criterion validity of each scale was also assessed by means of Spearman correlation coefficient between the total score of the questionnaires and the baseline characteristics as well as PD-related variables.

3.5.5 Factor analysis

In *study I*, the unidimensionality of the PDQ-8 questionnaire was checked by confirmatory principal factor analysis. An Eigen value of greater than 1 was considered as the best-fitted structure for the scale (Kaiser rule), however, the tendency to overextract the number of factors was also taken into account [123]. The Cattell scree plot was also drawn where the components were shown as the X-axis and the corresponding Eigen values as the Y-axis (*Figure 3*).

3.5.6 Diagnostic values

In *study II*, sensitivity and specificity were calculated based on the numbers of true positive, true negative, false positive and false negative answers for each single item of the screening instrument and the entire scale as well. Youden's index (ranges between 0-1) was calculated as: *(sensitivity + specificity)-1* [124], where a higher score indicated better diagnostic value. We applied the concept of clinical utility index (CUI) in order to select the optimal items for development of the new screening tool in *study II*. The corresponding CUI for each single screening item was calculated using an Excel calculator (http://www.psycho-oncology.info/cui.html). According to *Mitchell et al* [125], positive CUI is defined as: *sensitivity × positive predictive value (PPV)*, which represents the ability of the scale for ruling in the patients (case-finding). Negative CUI is calculated as: *specificity × negative predictive value (NPV)*, which shows how well the instrument or item is for ruling out the patients (screening). Both positive and negative CUIs range between 0 to 1 and a value of ≥ 0.81, ≥ 0.64, ≥ 0.49, <0.49 and <0.36 shows excellent, good, fair, poor and very poor utility, respectively [126]. In *study II*, the items with at least good negative utility (CUI$\geq$0.64) for screening of the parkinsonism from healthy condition were included in the new screening tool.

3.5.7 Receiver operating characteristics (ROC) curve analysis

In order to evaluate the discriminant ability of different screening questionnaires, ROC analysis was performed in *study II* to calculate the area under curve (AUC) and its 95% CI for each scale and compare their diagnostic accuracy to screen patients with parkinsonism. The optimal cut-off value of each screening scale was determined based on the CUI and Youden's index of

the recommended points through ROC analysis. In addition, we also implied ROC analysis in *study I* to compare the value of the total PDQ-8 and PDQ-39 scores to differentiate several PD-related conditions. Based on the median values in this study, UPDRS (total, part I and part III) scores, Hoehn & Yahr scale and Schwab & England ADL score were dichotomized into dummy variables as the predicted conditions in each of the ROC analysis. Then, comparisons were performed regarding the AUC of PDQ-8 and PDQ-39 scores and their corresponding 95% CI.

3.5.8 Univariate analyses

Chi square and Fisher's exact tests were used to compare relative frequency of categorical variables between study subgroups wherever appropriate. For between-group comparisons of continuous variables, independent samples *t* test was applied if the assumption of normal distribution was met. In case of skewed variables, the non-parametric Mann-Whitney *u* test was used. In all analytical procedures, a two-sided *p*-value <0.05 was considered as the statistical threshold to reject the beyond null hypothesis. Univariate associations between continuous variables were assessed using either Spearman or Pearson correlation tests.

3.5.9 Multivariate analysis

Multivariate linear and/or binary logistic regression models were performed for numeric or categorical outcome variables/conditions, respectively. For this purpose, significant univariate demographic variables were used for statistical adjustments, and the best representative variables from motor severity, motor subtypes and non-motor assessments were used as the main independent predictors/determinants. In all regression procedures, either beta coefficient or odds' ratio (OR) and their 95% CI were reported to present the strength of each association. We avoided including correlated indicators of one single entity. Tolerance index representing the proportion of variance for each independent variable that are not explained by other independent variables in the model, were calculated and were considered acceptable if >0.4. Conventionally, the variance inflation factor (VIF) (1/tolerance) was also reported and aimed to be <2.5 to prevent collinearity in the models. If the collinearity occurred, the variable with higher tolerance and larger standardized coefficient was kept and the other collinear variable was deleted from the regression model. In *study IV*, the two-way analysis of variance (ANOVA) was performed to adjust for the probable confounding effect of level of education on the main between-group comparisons.

3.5.10 Missing data imputation

Prior to perform structural equation modeling and cluster analyses and in order to avoid case-wise deletion and decreased statistical power, missing values of the database used for *study VI* were imputed. Only variables with at least 70% valid data and classified as *"missing at*

random" according to our judgment were eligible for imputation. Multiple imputation was carried out using independent regression equations where five different values were predicted for each single missing data. This methodology has been shown to have less biased parameter estimates than removing patients with missing values or other imputation methods such as the mean replacement [127]. As a result, a total of 95 single missing values were imputed accounting for 0.25% of the whole datasheet.

3.5.11 Cluster analysis

Two-step cluster analysis was applied to implement the clustering solution recommended by *Gasparoli et al* [89]. This clustering solution is based on current UPDRS-part II and part-III scores, dyskinesia and motor fluctuations to divide PD patients into two clinical phenotypes namely "*slow-progression*" and "*rapid-progression*", which we used in *study VI*.

3.5.12 Structural equation modeling (SEM)

This statistical method was applied in *study VI* to create a structural model for HRQoL in PD using the AMOS 22.0 module of the SPSS software version 22.0 (IBM., Chicago, IL, USA). Appropriate observed variables were firstly included in the SEM based on a hypothetical model and literature review. Three latent variables were placed in the SEM representing global motor, non-motor and HRQoL components. Afterwards, observed variables with non-significant estimates in the regression table were excluded. In the next step, recommended modifications to improve the structural model were added resulting in at least 20-unit decrease in the Chi square value of the whole model. In borderline cases when the difference between two models (with vs. without a specific modification) was small, the model with lower Bayesian information criterion (BIC) was selected. From each finalized SEM, the standardized regression weight (SRW) for each included component was reported. Fitness of each SEM was assessed using the absolute fit indices consisting of Normed Fit Index (NFI), Comparative Fit Index (CFI), Tucker-Lewis Index (TLI) and Root Mean Square Error of Approximation (RMSEA). An NFI, CFI and TLI value between 0.06 and 0.08 and RMSEA <0.08 indicate an acceptable model fit [128].

3.6 Ethical considerations

The study protocol for the whole PhD project was approved by the ethics committee of the neurology department at *Firoozgar Clinical Research Development Center (FCRDC)* (affiliated to Iran University of Medical Sciences) in Tehran, Iran. The application was accepted and issued with the number MT/140 on 25 June 2011. All procedures in research studies of this project were conducted in accordance with the ethical standards of the latest version of the *Helsinki Declaration*. Each participant was informed about the aims and

objectives of each study before participation and the completion of the questionnaire was voluntary in all studies. Furthermore, the identity of research participants was protected, since the data files were anonymous and all names were omitted. The FCRDC ethical committee was responsible for confirming that all collected data was kept confidential and no third-party had access to the collected personal health data.

4 RESULTS

4.1 Demography and baseline characteristics

4.1.1 Parkinson's disease patients

All demography, baseline, clinical and assessment characteristics of 157 IPD patients recruited from the Movement Disorders Clinic are summarized in *Table 5*. At the time of enrollments, the average age of participants was 61.4 (SD=11.2) *yrs* and 49 (31.2%) patients were female. In *study I*, *study II*, *study IV*, *study V* and *study VI*, either in part or entirely, we have used data from this population, which were mainly in the mild to moderate stages of PD with a mean UPDRS score of 32.2 (SD=18.1) and mean disease duration of 6.8 (SD=5.2) *yrs*.

Table 5. *Demography, baseline, clinical and assessment characteristics of the Parkinson's disease patients from the Movement Disorders Clinic (n=157)*

Characteristics	Value
➢ **Demography and General Information**	
Age-year (mean ± SD)	
Current	61.4 ± 11.2
At disease onset	54.7 ± 11.9
Gender NO (%)	
Female	49 (31.2)
Male	108 (68.8)
Level of Education NO (%)	
Illiterate	17 (11.0)
Primary and/ or secondary	37 (23.9)
High school/diploma	43 (27.7)
College and/ or university	58 (37.4)
Comorbidities NO (%)	
Hypertension	28 (18.1)
Ischemic heart disease	24 (15.7)
Osteoarthritis	19 (12.4)
Diabetes	20 (13.1)
Stroke/Transient ischemic attack	1 (0.7)
Chronic obstructive pulmonary disease	1 (0.7)
Total score (mean ± SD)	0.6 ± 1.0
Duration of Parkinson's Disease-year (mean ± SD)	6.8 ± 5.2
Levodopa Dose-mg (mean ± SD)	
Cumulative daily dose	864.7 ± 447.8
Weight-adjusted daily dose	12.6 ± 7.2
➢ **Assessments**	
UPDRS Score (mean ± SD)	
Part I- Mental	2.1 ± 2.4

Part II- ADL	11.7 ± 7.4
Part III- Motor	15.5 ± 9.2
Part IV- Complications	3.4 ± 2.8
Dyskinesia	0.9 ± 1.7
Fluctuations	1.7 ± 1.3
Total score	32.2 ± 18.1
Hoehn and Yahr Stage median (IQR)	2 (1.5)
Schwab and England Activities of Daily Living Score-(%) (mean ± SD)	80.5 ± 18.0
Anxiety Score (HADS) (mean ± SD)	6.8 ± 5.1
Depression Score (HADS) (mean ± SD)	5.1 ± 4.4
Fatigue Score (FSS) (mean ± SD)	4.5 ± 1.9
Nutritional Status (MNA) (mean ± SD)	
Screening score	12.7 ± 2.0
Assessment score	12.6 ± 1.9
Total score	25.2 ± 3.3
Psychosocial Functioning Score (SCOPA-PS)-(%) (mean ± SD)	25.9 ± 22.3
Quality of Life (PDQ-39) (mean ± SD)	
Dimension I-Mobility	28.2 ± 26.4
Dimension II-Activity of daily living (ADL)	26.4 ± 25.6
Dimension III-Emotional well-being	28.4 ± 23.6
Dimension IV-Stigma	21.9 ± 25.2
Dimension V-Social support	11.5 ± 20.3
Dimension VI-Cognitions	17.9 ± 20.1
Dimension VII-Communication	15.1 ± 19.5
Dimension VIII-Bodily Discomfort	22.1 ± 23.0
Parkinson's disease summary index (PDSI) (mean ± SD)	21.2 ± 15.4

SD: standard deviation; IQR: interquartile range

4.1.2 Community-based population

In *study III*, 12,907 (66.2%) women and 6,593 (33.8%) men with the mean age of 56.5 (SD=10.2) *yrs* ranging between 30 and 95 *yrs* participated in the community-based door-to-door survey. Majority of the study population (81.8%, n=15,147) were married and less than a quarter (22.4%, n=3,989) were retired. Hypertension (29.9%, n=5,838), osteoarthritis (18.0%, n=3,519) and diabetes (18.0%, n=3,516) were recorded as the commonest morbidities, respectively.

4.2 Validations studies

In the validation phase of the project, five questionnaires were evaluated consisting of FSS, SCOPA, MNA, PDQ-39 and PDQ-8. For this purpose, we performed four validation studies, which are briefly described afterwards. Validity and reliability findings of each of these studies are listed in *Table 6*.

Table 6. *Validity and reliability of the Persian-translated versions of the questionnaires used in this project*

Questionnaire	Sample Size	Reliability		Validity	
		Internal Consistency Spearman r (Range)	Internal Consistency Cronbach's α (95% CI)	Correlation Coefficient UPDRS-total score (Pearson r)	Correlation Coefficient Hoehn & Yahr (Pearson r)
Fatigue Severity Scale (FSS)	90	0.76-0.92	0.96 (0.95-0.97)	0.55	0.48
Scales for Outcomes in Parkinson's Disease-psychosocial Questionnaire (SCOPA-PS)	110	0.55-0.77	0.87 (0.83-0.90)	0.55	0.34
Mini Nutritional Assessment (MNA)	143	0.03*-0.53	0.70 (0.62-0.77)	-0.63	-0.43
Parkinson's Disease Questionnaire-39 items (PDQ-39)	114	0.57-0.87	0.94 (0.92-0.95)	0.64	0.44
Parkinson's Disease Questionnaire-8 items (PDQ-8)	114	0.46-0.70	0.74 (0.66-0.81)	0.59	0.38

CI: confidence interval
All coefficients are statistically significant (p-value<0.05) except for Spearman internal consistency of two items in the MNA questionnaire (*).

4.2.1 Fatigue severity scale (FSS)

Using data on 90 patients with IPD recruited from the Movement Disorder Clinic, the internal consistency coefficient of the Persian-translated FSS was shown to be larger than 0.8 for all of the items and the total Cronbach's alpha was 0.96 (95% CI: 0.95-0.97) [110]. As shown in *Table 7*, the FSS had high Cronbach's alpha coefficient (≥0.93) within all subgroups of PD patients regarding age groups, sex, educational level and disease severity assessed by the Hoehn & Yahr stage. The total score of the FSS was significantly valid to discriminate patients with more severe disability (Hoehn & Yahr stage>2) from those with less severity (Hoehn & Yahr stage≤2) [AUC=0.81 (95% CI: 0.72-0.90)] [110].

Table 7. *Reliability (Cronbach's α) of the Parkinson Disease Questionnaire (PDQ-8) and Fatigue Severity Scale (FSS) questionnaires within various subgroups of Iranian Parkinson's disease patients*

Subgroups		Cronbach's α Coefficient	
		PDQ-8	FSS
Age Group	<65 yr	0.65 (0.51-0.76)	0.97 (0.95-0.98)
	≥65 yr	0.84 (0.76-0.90)	0.95 (0.92-0.97)
Gender	Female	0.69 (0.47-0.85)	0.93 (0.88-0.96)
	Male	0.76 (0.67-0.83)	0.97 (0.95-0.98)
Educational Level	Illiterate/Primary/ Secondary school	0.77 (0.68-0.84)	0.94 (0.92-0.96)
	College/University	0.58 (0.35-0.74)	0.98 (0.97-0.99)
Hoehn & Yahr Stage	≤2	0.71 (0.60-0.80)	0.95 (0.93-0.97)
	>2	0.75 (0.61-0.86)	0.94 (0.90-0.97)

All coefficients are statistically significant (p-value<0.001)

4.2.2 Scales for outcomes in Parkinson's disease-psychosocial questionnaire (SCOPA-PS)

SCOPA-PS was validated in 110 Iranian patients with IPD. Independent native speakers approved content validity through translation and back-translation method. The overall Cronbach's alpha coefficient for reliability was 0.87 (95% CI: 0.83-0.90). In item-specific analysis, the highest and lowest internal consistency was observed in item-7 on "*asking for help*" (r=0.765) and item-5 on "*sexual problems*" (r=0.553), respectively [112]. *Table 8* shows the results for the linear regression model to determine the factors independently affect total score of the SCOPA-PS questionnaire in recruited IPD patients. After exclusion of the non-significant variables, a regression model was achieved (R^2=0.703, p<0.001) including HADS anxiety (B=0.71, p=0.020) and depression (B=1.53, p<0.001) scores, and the cognition (B=0.17, p=0.047), stigma (B=0.21, p<0.001) and mobility (B=0.21, p=0.003) domains of the PDQ-39 questionnaire.

4.2.3 Mini-nutritional assessment (MNA)

Another validation study was performed on 143 IPD patients to evaluate validity and reliability of the Persian-version of the MNA. The Cronbach's alpha coefficient for the entire MNA was calculated as 0.70 (95% CI: 0.62-0.77). Nevertheless, reliability coefficient was significantly higher among the younger patients (age <65 *yrs*) [0.75 (95% CI: 0.67-0.82) vs. 0.55 (95 CI%: 0.37-0.71), p<0.05]. The total score of the MNA significantly correlated with weight (r=0.427, p<0.001), MAC (r=0.268, p=0.001) and CC (r=0.285, p=0.001) and could discriminate IPD patients with BMI ≥24 kg/m^2 (AUC=0.71, p<0.001). The cut-off value of 26 for the total MNA

score had 58% sensitivity and 82% specificity for this discrimination [113].

Table 8. *Multivariate linear regression model of the independent scales/variables relating to the total score of the SCOPA-PS questionnaire in Iranian Parkinson's disease patients (n=110) (R^2=0.703, p<0.001)*

Scales/ Variables	Unstandardized Coefficients		Standardized Coefficients	*t*	*p*-value	95% CI for B	
	B	SEM	Beta			Lower Bound	Upper Bound
HADS Depression	1.534	0.408	0.305	3.76	<0.001*	0.723	2.345
PDQ-39 Cognition	0.173	0.086	0.161	2.02	0.047*	0.002	0.344
PDQ-39 Stigma	0.208	0.056	0.243	3.75	<0.001*	0.098	0.319
PDQ-39 Mobility	0.215	0.070	0.253	3.08	0.003*	0.076	0.355
HADS Anxiety	0.711	0.301	0.180	2.36	0.020*	0.113	1.310
Constant	-1.501	2.029	-	-0.74	0.461	-5.536	2.533

SEM: standard error of mean, CI: confidence interval
* Statistically significant (p-value<0.05)

4.2.4 Parkinson's disease questionnaire (PDQ)

In *study I*, psychometric properties of the Persian-translated version of the PDQ-8 questionnaire were assessed in 114 IPD patients from our Movement Disorders Clinic. *Figure 3* shows the Scree plot for PDQ-8 questionnaire demonstrating one-factor structure as the best fitted model, which explained 37.31% of the variance of the PDQ-8 scores (Eigen value=2.98).

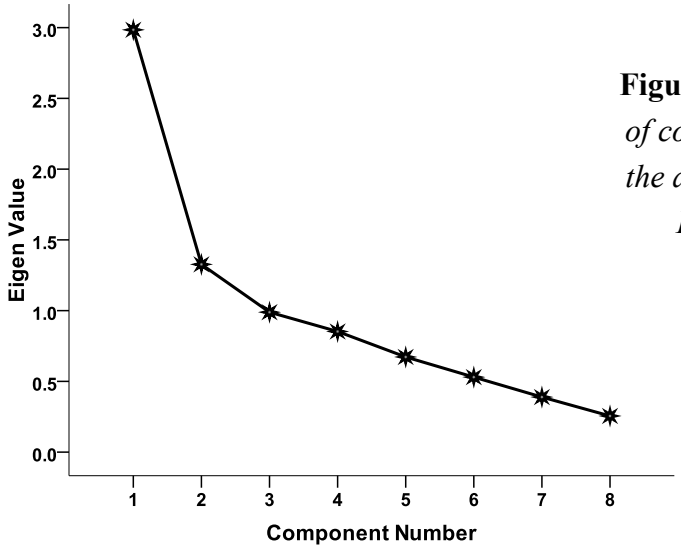


Figure 3. *Scree plot to evaluate the number of components that best fit the variances of the answers to the PDQ-8 questionnaire in Iranian Parkinson disease patients*

Both PDQ-39 [Cronbach's alpha=0.94 (95% CI: 0.92-0.95)] and PDQ-8 [Cronbach's alpha=0.74 (95% CI: 0.66-0.81)] questionnaires had high reliability coefficients. The overall reliability of the PDQ-8 (Cronbach's alpha coefficient) would not further improve by replacement of its items with other questions with higher internal consistency within each corresponding dimension in the original PDQ-39 [115]. The Persian-version of the PDQ-8 was shown to be a reliable instrument within different subgroups of IPD patients regarding age groups, sex, educational level and Hoehn & Yahr stage (*Table 7*). As illustrated in *Figure 4*, the scores of both PDQ-8 and PDQ-39 demonstrated significant discriminant values to distinguish different severity-related dummy conditions (all $p<0.001$). The mental scale of the UPDRS (part-I) was the only variable where the calculated AUC was larger for the PDQ-8 to discriminate the patients with score >1 ($AUC_{PDQ-8}=0.812$, $AUC_{PDQ-39}=0.801$; *Figure 4-A*). By contrast, the score from PDQ-39 had larger AUC to discriminate IPD patients with UPDRS-motor domain (part-III) score >13 ($AUC_{PDQ-8}=0.632$, $AUC_{PDQ-39}=0.670$; *Figure 4-B*), UPDRS total score >30 ($AUC_{PDQ-8}=0.762$, $AUC_{PDQ-39}=0.791$; *Figure 4-C*), Hoehn & Yahr Stage >2 ($AUC_{PDQ-8}=0.706$, $AUC_{PDQ-39}=0.764$; *Figure 4-D*) and Schwab & England ADL Score ≤80% ($AUC_{PDQ-8}=0.737$, $AUC_{PDQ-39}=0.775$; *Figure 4-E*).

4.3 Development of the screening instrument

In *study II*, a comprehensive list of 25 potential screening items for parkinsonism (*Table 9*) was filled in 147 patients with IPD, 10 patients with atypical parkinsonism (AP), 7 patients with essential tremor (ET), 14 patients with dystonia, 19 patients with other neurologic disorders and 110 healthy controls. In most analyses, data from patients with IPD and atypical parkinsonism were merged to make a single group of patients with parkinsonism (n=157). As it is shown in *Table 9*, six items on "*tremor & shaking*" [$CUI^{-}=0.734$ (95% CI: 0.730-0.738)], "*troublesome arm swing*" [$CUI^{-}=0.702$ (95% CI: 0.698-0.706)], "*stiffness & rigidity*" [$CUI^{-}=0.670$ (95% CI: 0.666-0.675)], "*feet stuck to floor*" [$CUI^{-}=0.667$ (95% CI: 0.663-0.671)], "*slower daily activity*" [$CUI^{-}=0.649$ (95% CI: 0.644-0.654)] and "*troublesome buttoning*" [$CUI^{-}=0.643$ (95% CI: 0.639-0.647)] demonstrated good utility (CUI≥0.64) to be included in the new screening tool for parkinsonism with the highest negative CUIs, respectively. Some other symptoms such as "*changes in speech*", "*smaller handwriting*", "*shuffling & small steps*", "*stooped posture*" and "*inexpressive face*" showed a fair utility with a negative CUI ranging between 0.563 and 0.622.

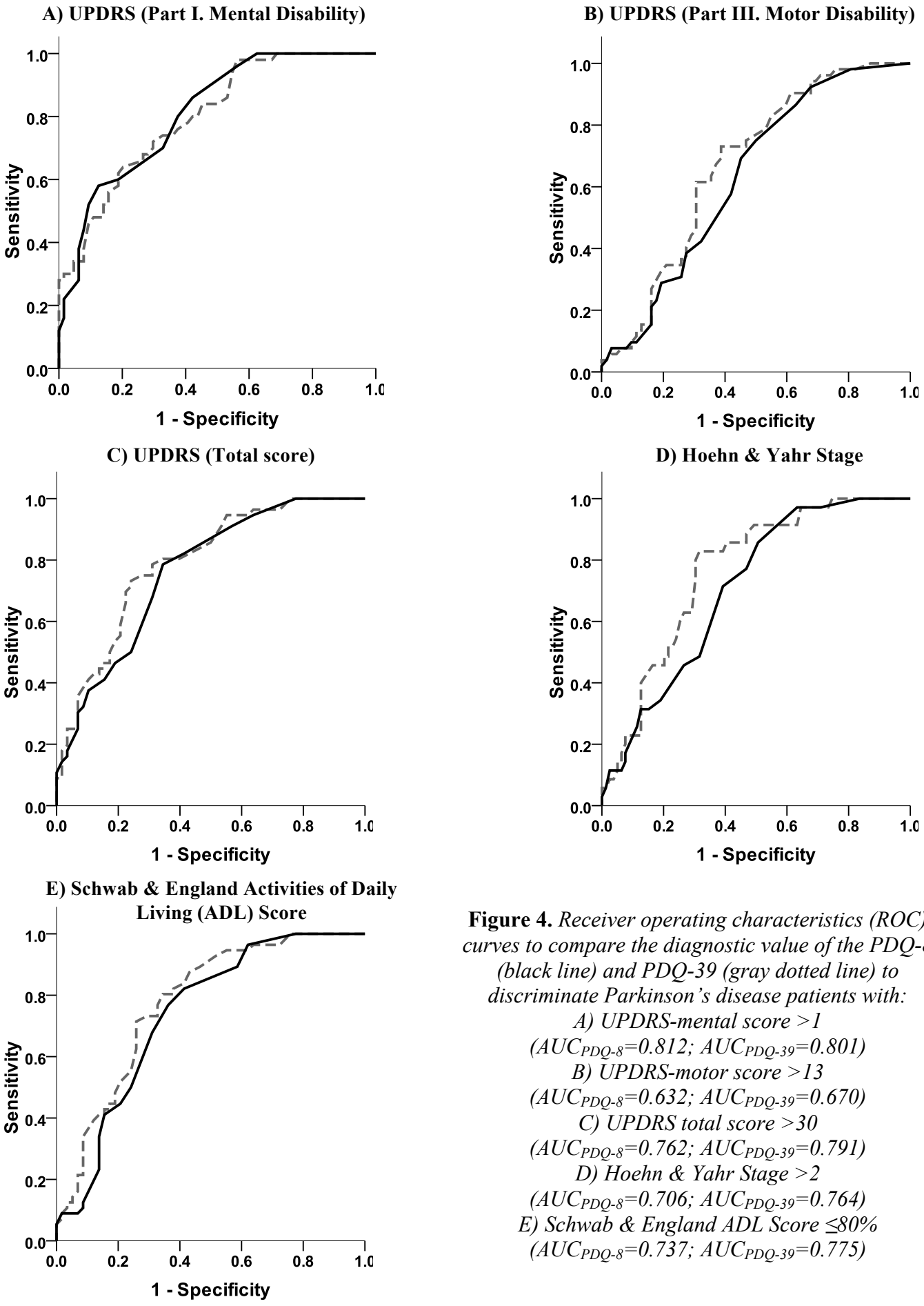


Figure 4. *Receiver operating characteristics (ROC) curves to compare the diagnostic value of the PDQ-8 (black line) and PDQ-39 (gray dotted line) to discriminate Parkinson's disease patients with:*
A) UPDRS-mental score >1
(AUC_{PDQ-8}=0.812; AUC_{PDQ-39}=0.801)
B) UPDRS-motor score >13
(AUC_{PDQ-8}=0.632; AUC_{PDQ-39}=0.670)
C) UPDRS total score >30
(AUC_{PDQ-8}=0.762; AUC_{PDQ-39}=0.791)
D) Hoehn & Yahr Stage >2
(AUC_{PDQ-8}=0.706; AUC_{PDQ-39}=0.764)
E) Schwab & England ADL Score ≤80%
(AUC_{PDQ-8}=0.737; AUC_{PDQ-39}=0.775)

Following selection of the best items, a new screening tool was developed consisting of the six symptoms with good negative CUI [88]. However, the discriminative performance of our new screening tool to distinguish patients with parkinsonism from healthy individuals was assessed in five different formats:

1) Crude score of the 6-item instrument consisting of symptoms with good negative CUI
2) Crude score of the 11-item instrument consisting of symptoms with either good or fair negative CUI
3) Weighted score of the 6-item instrument using CUI
4) Weighted score of the 6-item instrument using regression model [resulted in a 4-item weighted version as: 2*("*stiffness & rigidity in legs*")+5*("*tremor & shaking*")+5*("*troublesome arm swing*")+5*("*feet stuck to floor*")]
5) Weighted score of the 6-item instrument based on prevalence

Using ROC analysis, the optimal cut-off values for discrimination were calculated for each format (*Figure 5*).

Having included questions from several different instruments, we were able to imply the same procedures on previously introduced screening tools for parkinsonism on our single database to compare their discriminative capacity (*Figure 6*).

Results from ROC analysis confirmed that our new 6-item screening instrument had the highest AUC [0.977 (95% CI: 0.963-0.992)] to discriminate IPD patients from healthy individuals compared to other screening tools that were assessed in our study. Furthermore, the new screening instrument had significant AUC to distinguish parkinsonism with different severities from healthy condition as follows:

1) Hoehn & Yahr ≤ 1 [AUC=0.952 (95% CI: 0.918-0.986)]
2) $1 <$ Hoehn & Yahr ≤ 2 [AUC=0.985 (95% CI: 0.971-0.999)]
3) Hoehn & Yahr > 2 [AUC=0.994 (95% CI: 0.985-1)]

Table 9. *Diagnostic values and Clinical utility index (CUI) of each single item for screening (ruling-out) or case-finding (ruling-in) of parkinsonism from healthy condition [The range mentioned in parenthesis represents the 95% confidence interval (CI) of the estimations]*

NO.	Item	Sensitivity (%)	Specificity (%)	Youden Index	Positive CUI	Negative CUI
1	Impaired Consciousness	16.9 (11.5-23.9)	95.3 (88.9-98.2)	0.12	0.142 (0.135-0.148) ××	0.423 (0.418-0.427) ×
2	Uncontrolled Movements of Limbs	71.7 (63.7-78.6)	83.6 (75.1-89.8)	0.55	0.615 (0.611-0.620) ✓	0.570 (0.565-0.575) ✓
3	Changes in Speech	56.9 (48.6-64.8)	92.7 (85.7-96.6)	0.50	0.521 (0.515-0.526) ✓	0.563 (0.558-0.568) ✓
4	Paralysis of Face	NS	NS	-	NS	NS
5	Drooling from Mouth	19.0 (13.2-26.3)	95.5 (89.2-98.3)	0.15	0.162 (0.155-0.169) ××	0.438 (0.433-0.442) ×
6	Weakness of Limbs	NS	NS	-	NS	NS
7	Sensory Changes in Limbs	NS	NS	-	NS	NS
8	Stiffness & Rigidity in Legs	88.9 (82.5-93.2)	80.0 (71.1-86.8)	0.69	0.765 (0.763-0.768) ✓✓	0.670 (0.666-0.675) ✓✓
9	Tremor & Shaking	85.8 (79.1-90.7)	89.9 (82.3-94.6)	0.76	0.793 (0.790-0.795) ✓✓	0.734 (0.730-0.738) ✓✓
10	Smaller Handwriting	65.0 (56.3-72.8)	93.8 (86.5-97.5)	0.59	0.609 (0.603-0.614) ✓	0.614 (0.609-0.619) ✓
11	Trouble in Arising from Chair	42.5 (34.6-50.7)	82.7 (74.1-89.0)	0.25	0.329 (0.322-0.335) ××	0.421 (0.415-0.426) ×
12	Softer Voice	22.1 (16.0-29.6)	92.6 (85.5-96.5)	0.15	0.179 (0.172-0.186) ××	0.421 (0.416-0.425) ×
13	Shoulder Pain	NS	NS	-	NS	NS
14	Troublesome Buttoning	63.0 (54.8-70.5)	98.2 (92.9-99.7)	0.61	0.617 (0.612-0.622) ✓	0.643 (0.639-0.647) ✓✓
15	Shuffling & Small Steps	69.0 (61.0-76.1)	91.2 (84.6-96.0)	0.60	0.637 (0.633-0.641) ✓	0.622 (0.618-0.627) ✓
16	Troublesome Arm Swing	72.7 (64.7-79.5)	98.1 (92.6-99.7)	0.71	0.714 (0.710-0.717) ✓✓	0.702 (0.698-0.706) ✓✓
17	Poor Balance	445.8 (37.8-54.0)	82.7 (74.1-89.0)	0.29	0.361 (0.355-0.368) ×	0.430 (0.425-0.435) ×

18	Feet Stuck to Floor	66.4 (58.3-73.8)	98.2 (92.9-99.7)	0.65	0.652 (0.647-0.656) ✓✓	0.667 (0.663-0.671) ✓✓
19	Stooped Posture	59.4 (51.2-67.1)	92.7 (85.7-96.6)	0.52	0.546 (0.541-0.551) ✓	0.573 (0.569-0.578) ✓
20	Changes in Smelling Ability	23.5 (17.2-31.2)	90.0 (82.4-94.7)	0.14	0.180 (0.173-0.187) ××	0.413 (0.408-0.417) ×
21	Screaming Nightmares	42.6 (34.8-50.8)	74.5 (65.2-82.2)	0.17	0.299 (0.293-0.305) ××	0.357 (0.352-0.363) ××
22	Troublesome Concentration & Memory	NS	NS	-	NS	NS
23	Slower Daily Activity	85.8 (79.1-90.7)	80.9 (72.1-87.5)	0.67	0.741 (0.738-0.744) ✓✓	0.649 (0.644-0.654) ✓✓
24	Inexpressive Face	48.3 (40.0-56.7)	96.4 (90.4-98.8)	0.45	0.461 (0.455-0.468) ×	0.558 (0.554-0.563) ✓
25	Troublesome Walking	69.4 (61.1-76.7)	72.7 (63.3-80.6)	0.42	0.544 (0.540-0.549) ✓	0.465 (0.459-0.472) ×

CUI: clinical utility index, NS: Not significant
×× very poor utility, × poor utility, ✓ fair utility, ✓✓ good utility

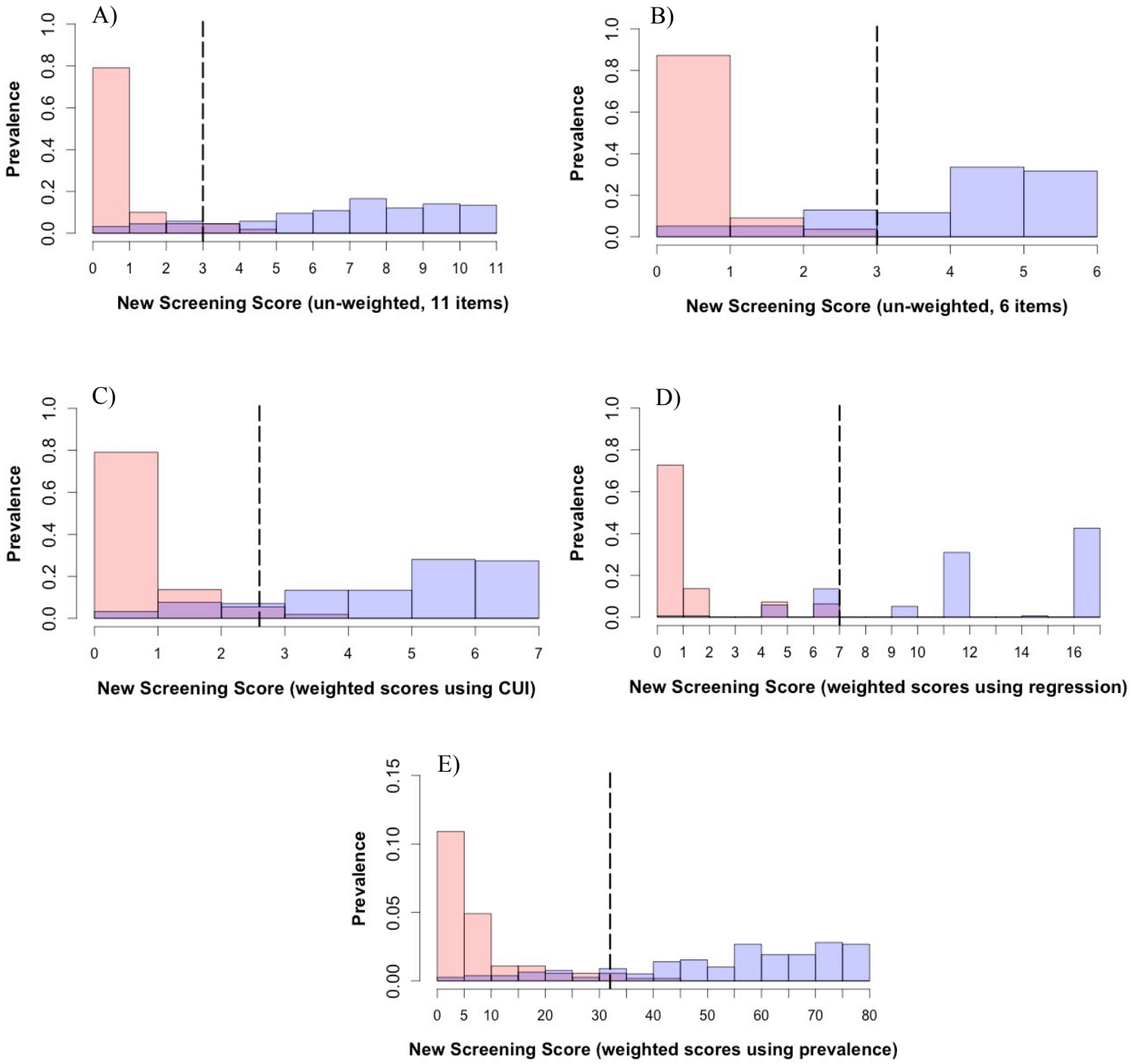
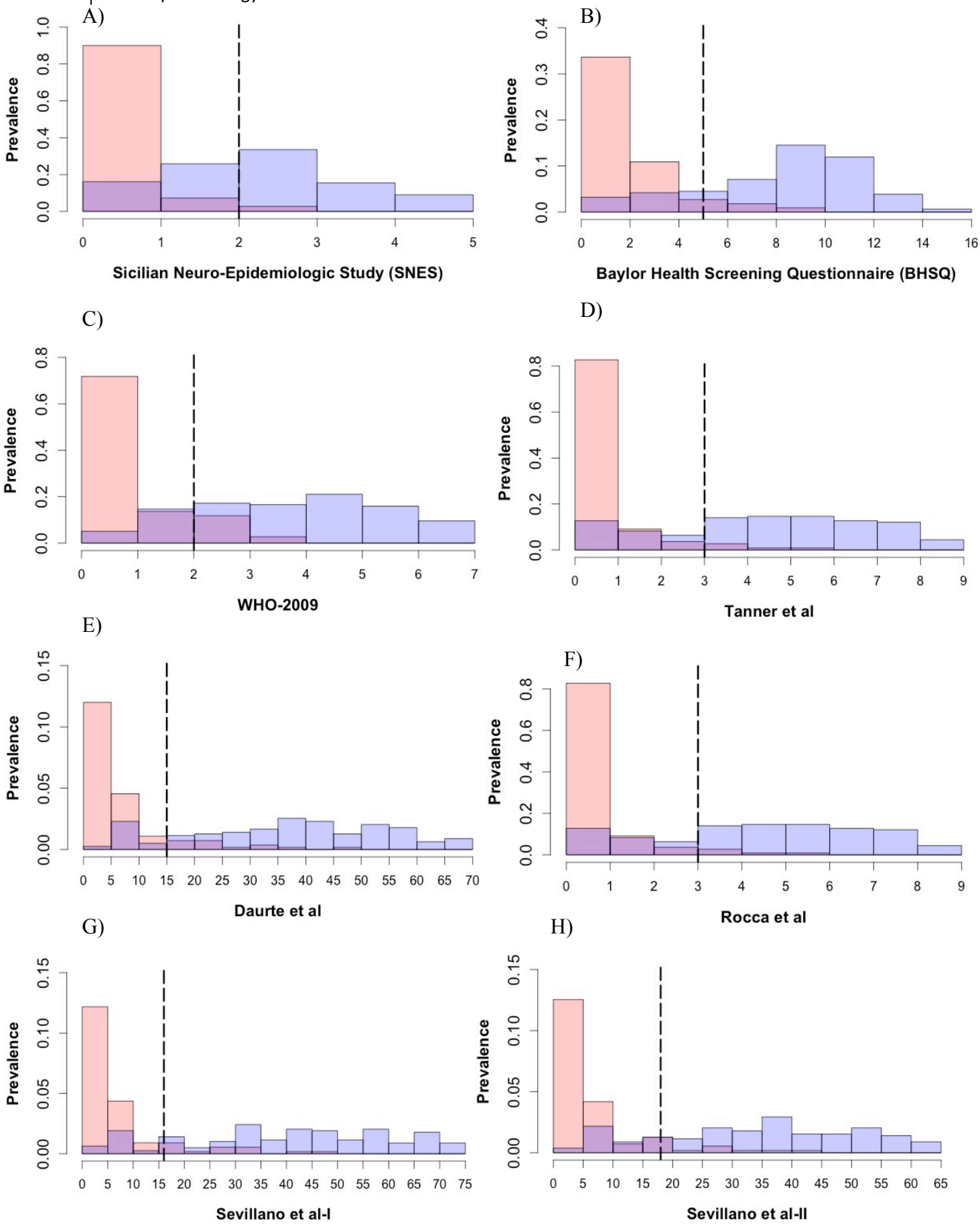


Figure 5. *Overlaid histogram plots of different formats/modifications of the new screening instrument's score to discriminate parkinsonism (blue columns) from healthy condition (pink columns) in recruited participants (total n=267). The overlaid purple columns represent either false negative or false positive categorized individuals, and the dashed black lines show the optimal cut-point value for discrimination in each condition.*


A)
Prevalence
Sicilian Neuro-Epidemiologic Study (SNES)
B)
Prevalence
Baylor Health Screening Questionnaire (BHSQ)
C)
Prevalence
WHO-2009
D)
Prevalence
Tanner et al
E)
Prevalence
Daurte et al
F)
Prevalence
Rocca et al
G)
Prevalence
Sevillano et al-I
H)
Prevalence
Sevillano et al-II

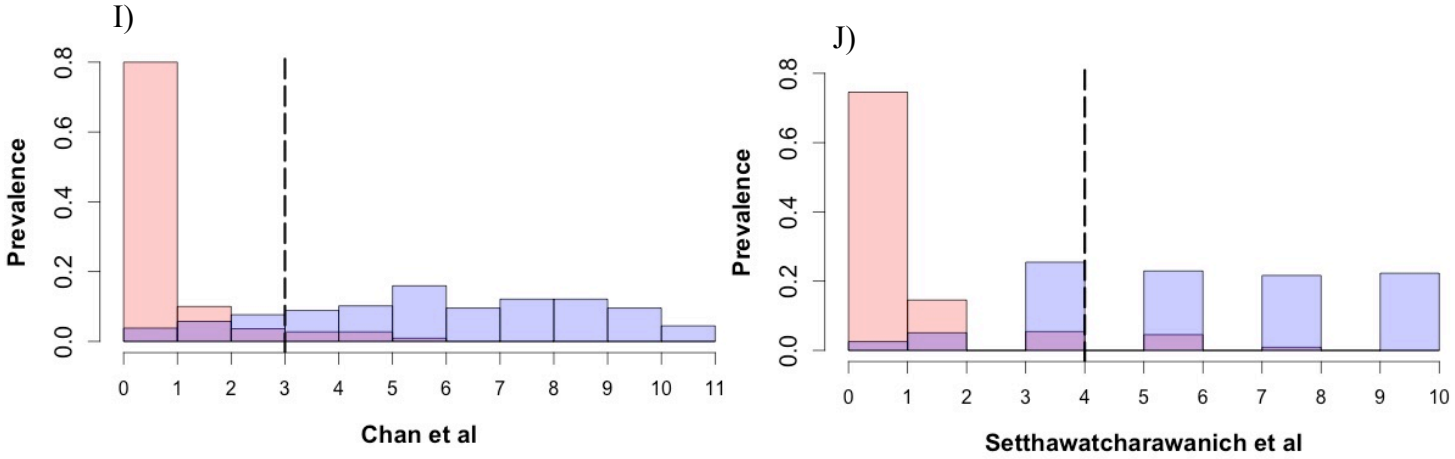


Figure 6. *Overlaid histogram plots of different screening instruments' scores to discriminate parkinsonism (blue columns) from healthy condition (pink columns) evaluated in our single database (total n=267). The overlaid purple columns represent either false negative or false positive categorized individuals and the dashed black lines show the optimal cut-point value for discrimination in each instrument.*

4.4 Prevalence of parkinsonism

Using the new screening tool developed in *study II*, 157 individuals with an average age of 64.5 (SD=10.9) *yrs* who were recruited through the community-based door-to-door survey were positively screened for parkinsonism in *study III*. This resulted in an age- and sex-adjusted prevalence rate of 222.9/100,000 (95% CI: 160-300) and 285/100,000 (95% CI: 240-329) based on real Tehran population and the "*WHO World Standard Population*", respectively [42]. Other than the new 6-item instrument, we also calculated the prevalence rate for positively screened cases by other tools. The standardized prevalence rate based on the "*WHO World Standard Population*" varied between 104.2/100,000 (95% CI: 87.9-120.5) (using *Tanner et al* items [104]) and 296.0/100,000 (95% CI: 249.7-342.4) (using the SNES tool). The male/female ratio of probable parkinsonism was 1.62 and a significant increase in the screening rate was observed by increasing age (p=0.026 for trend, *Figure 7*).

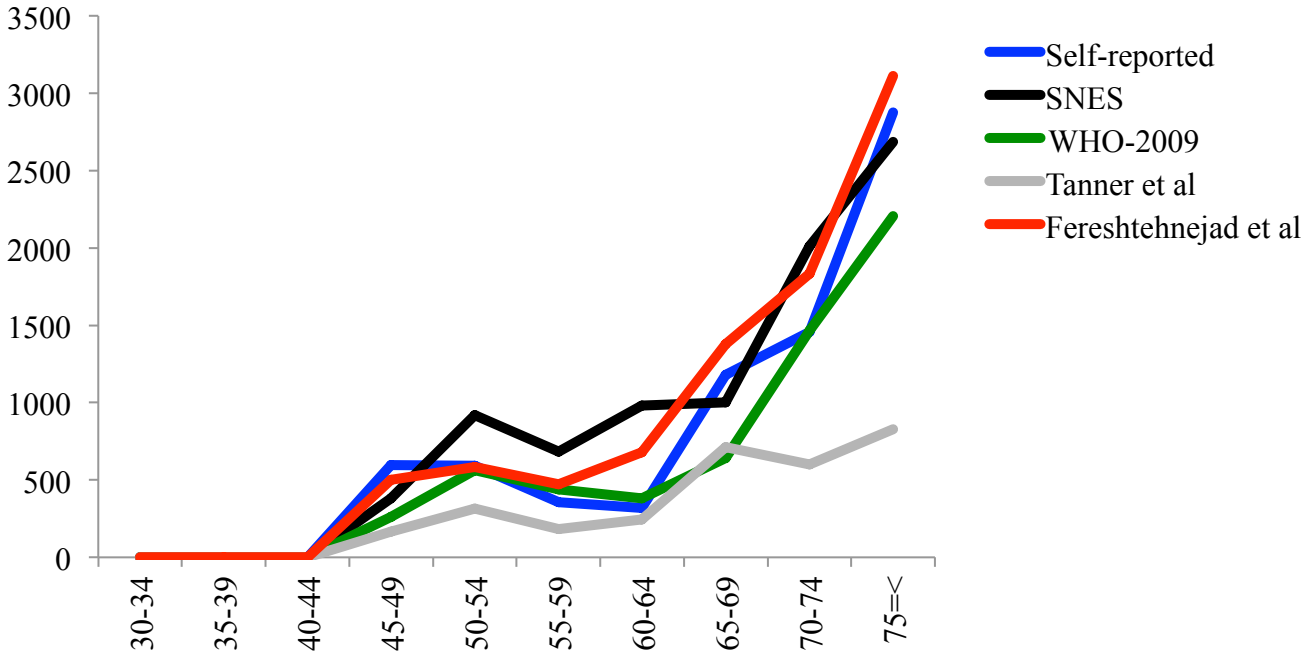


Figure 7. *Age- and sex-adjusted rates (/100,000) of screened cases suspicious of parkinsonism using different screening instruments in each age category*

4.5 Nutritional status in Parkinson's disease

4.5.1 Prevalence of malnutrition

Nutritional status of the IPD patients enrolled from the Movement Disorders Clinic was assessed and compared with a group of age- and sex-matched controls using the Persian-translated version of the MNA and anthropometric measurements in *study IV*. No significant difference was found neither in the mean of total MNA score [25.1 (SD=3.4) in IPD patients vs. 24.4 (SD=3.8) in controls, p=0.094] nor in the prevalence of malnutrition [2.1% (n=3) in IPD patients vs. 2.0% (n=3), p=0.228] between the two study groups. Another 37 (25.9%) IPD patients and 51 (35.2%) controls were at risk of malnutrition (p=0.228) [55]. Detailed comparisons of anthropometric measurements are shown in *Figure 8* demonstrating no significant difference in the categories of BMI, MAC and CC between the IPD and control groups (all p>0.05).

Although case and control groups were matched based on the mean age and gender distribution, educational level was significantly different between two study groups. Therefore, further subgroup analysis followed by multivariate statistic was performed to assess the probable confounding effect of this variable. As shown in *Figure 9*, among illiterate individuals the mean MNA score was significantly higher in IPD patients [24.19 (SD=2.18) vs.

21.93 (SD=3.42), *p*=0.040], whereas among the ones with high school or college/university education the mean of total MNA score was higher in the control group. Nevertheless, even after adjustment for educational level by multivariate analysis, no significant difference was found in the average of total MNA score between IPD patients and the controls (*p*=0.434).

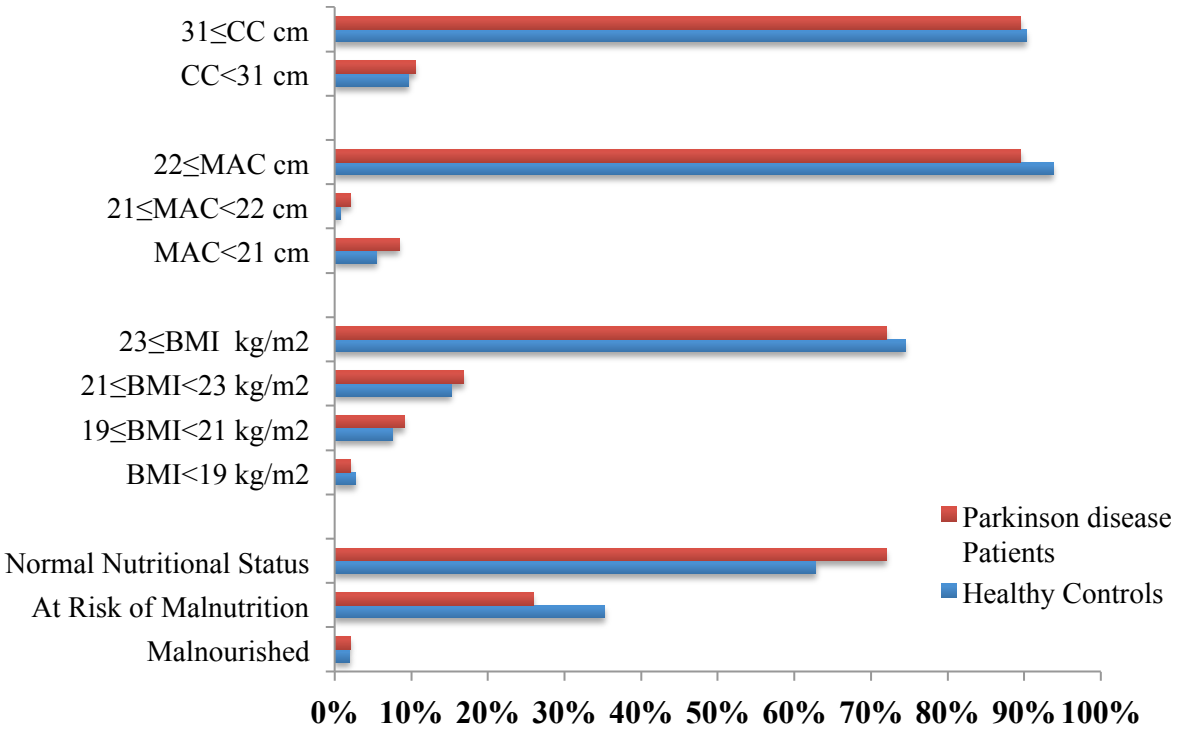


Figure 8. *Distribution of different categories of anthropometric measurements consisting of calf circumference (CC, p=0.814), mild-arm circumference (MAC, p=0.363) and body mass index (BMI, p=0.919) and the whole nutritional status based on the total score of Mini Nutritional Assessment (MNA, p=0.228) in healthy controls versus Parkinson disease patients*

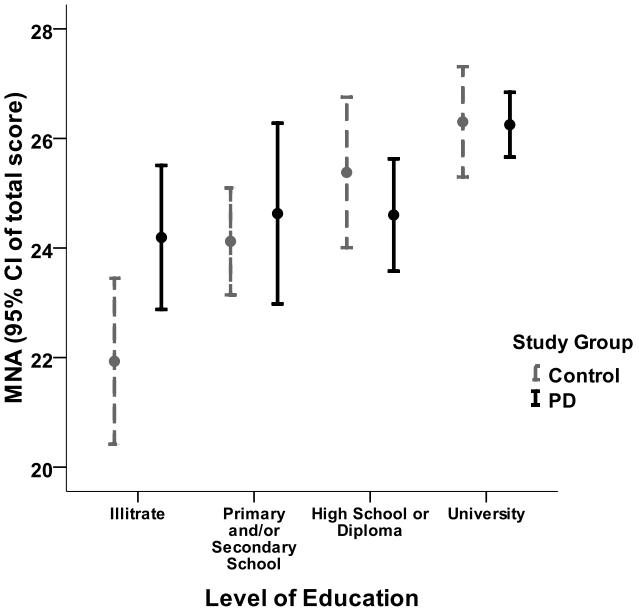


Figure 9. *Error bars for comparison of the total score of Mini Nutritional Assessment (MNA) between Parkinson disease patients and healthy controls within the subgroups of educational level (Illiterate: p=0.040; primary and/or secondary school: p=0.574; high school/diploma: p=0.351; university: p=0.921) (* statistical significant difference)*

4.5.2 Determinants of malnutrition

In *study V*, the association between nutritional status and a comprehensive list of motor and non-motor features of PD was evaluated in 146 IPD patients from the Movement Disorders Clinic. Forty patients were either malnourished or at risk of malnutrition. *Table 10* shows the findings for univariate comparisons of the baseline, HRQoL, disease severity and psychiatric features between the two groups of IPD patients regarding nutritional status. IPD patients with abnormal nutritional status had a significantly higher score not only for the entire UPDRS [45.9 (SD=18.0) vs. 26.4 (SD=13.6), $p<0.001$] but also for all of its parts (all $p<0.05$). Among the NMS, more severe anxiety [8.8 (SD=5.2) vs. 5.9 (SD=4.9), $p=0.002$], depression [9.0 (SD=4.2) vs. 3.6 (SD=3.5), $p<0.001$] and fatigue [5.4 (SD=1.5) vs. 4.2 (SD=2.0), $p<0.001$] were recorded in those with abnormal nutritional status. Except for stigma, all other domains of HRQoL were significantly poorer among those with abnormal nutritional status (all $p<0.05$) [73]. Even though total MNA score was not significantly associated with patients' age (r=0.021, $p=0.805$), it inversely correlated with disease duration (r=-0.249, $p=0.002$) such that those with longer PD duration had worse nutritional status (*Figure 10*).

Two multivariate regression models were applied to investigate the independent predictors of total MNA score (as a continuous outcome) and being either malnourished or at risk of malnutrition (as a binary outcome). As it is summarized in *Table 11*, depression (standardized coefficient=-0.352, $p<0.001$), total UPDRS score (standardized coefficient=-0.313, $p<0.001$), patients' sex (standardized coefficient=-0.196, $p=0.003$) and weight-adjusted daily levodopa dosage (standardized coefficient=-0.190, $p=0.006$) were the strongest independent determinants of total MNA score after multivariate adjustments. Results from model 2 revealed that each unit of increase in the Hoehn and Yahr stage and depression score accompanied with a 2.4-time (95% CI: 1.3-4.5, $p=0.007$) and 1.4-time (95% CI: 1.2-1.6, $p<0.001$) higher likelihood of being malnourished or at risk of malnutrition in IPD patients, respectively [73].

Table 10. *Comparison of the mean [standard deviation (SD)] scores of different motor, non-motor and quality of life (PDQ-39) scales between subgroups of Parkinson disease (PD) patients regarding nutritional status (MNA)*

Scale	Domain	Malnourished or at risk of malnutrition (n=40)	Normal nutritional status (n=106)	*p*-value (*t* test)
Baseline	Age (yr)	61.3 (12.3)	61.3 (9.8)	0.982
	Disease duration (yr)	8.2 (6.9)	6.2 (4.6)	0.045*
	Body mass index (BMI) (kg/m^2)	23.9 (3.8)	26.6 (4.3)	0.001*
	Daily levodopa dose (mg)	817 (450)	841 (490)	0.789
PDQ39	Mobility	45.6 (26.6)	19.4 (20.7)	<0.001*
	Activities of daily living (ADL)	38.4 (28.9)	18.0 (17.9)	<0.001*
	Emotional well-being	41.3 (22.4)	22.1 (20.8)	<0.001*
	Stigma	22.0 (24.4)	21.5 (25.4)	0.913
	Social support	13.0 (17.2)	5.1 (10.9)	0.016*
	Cognitive impairment	25.5 (20.5)	13.5 (16.6)	<0.001*
	Communication	24.6 (23.9)	10.3 (13.6)	0.001*
	Bodily discomfort	32.5 (20.3)	16.4 (19.6)	<0.001*
Disease Severity	UPDRS: Part I-mental	3.8 (3.2)	1.3 (1.4)	<0.001*
	UPDRS: Part II-ADL	15.9 (7.8)	9.4 (5.8)	<0.001*
	UPDRS: Part III-motor	20.6 (10.1)	13.3 (7.4)	<0.001*
	UPDRS: Part IV-complications a. Dyskinesia b. Wearing off	5.1 (3.4) 1.7 (2.5) 2.3 (1.4)	2.9 (2.2) .8 (1.4) 1.5 (1.2)	<0.001* 0.042* 0.003*
	UPDRS: Total	45.9 (18.0)	26.4 (13.6)	<0.001*
	Hoehn & Yahr stage#	2.5 (.8)	1.8 (.8)	<0.001*
	Schwab & England stage (%)	71.2 (19.6)	85.7 (13.9)	<0.001*
HADS	Anxiety	8.8 (5.2)	5.9 (4.9)	0.002*
	Depression	9.0 (4.2)	3.6 (3.5)	<0.001*
FSS	Fatigue	5.4 (1.5)	4.2 (2.0)	<0.001*

Values are presented as median [interquartile range (IQR)]

* Statistically significant (p-value<0.05)

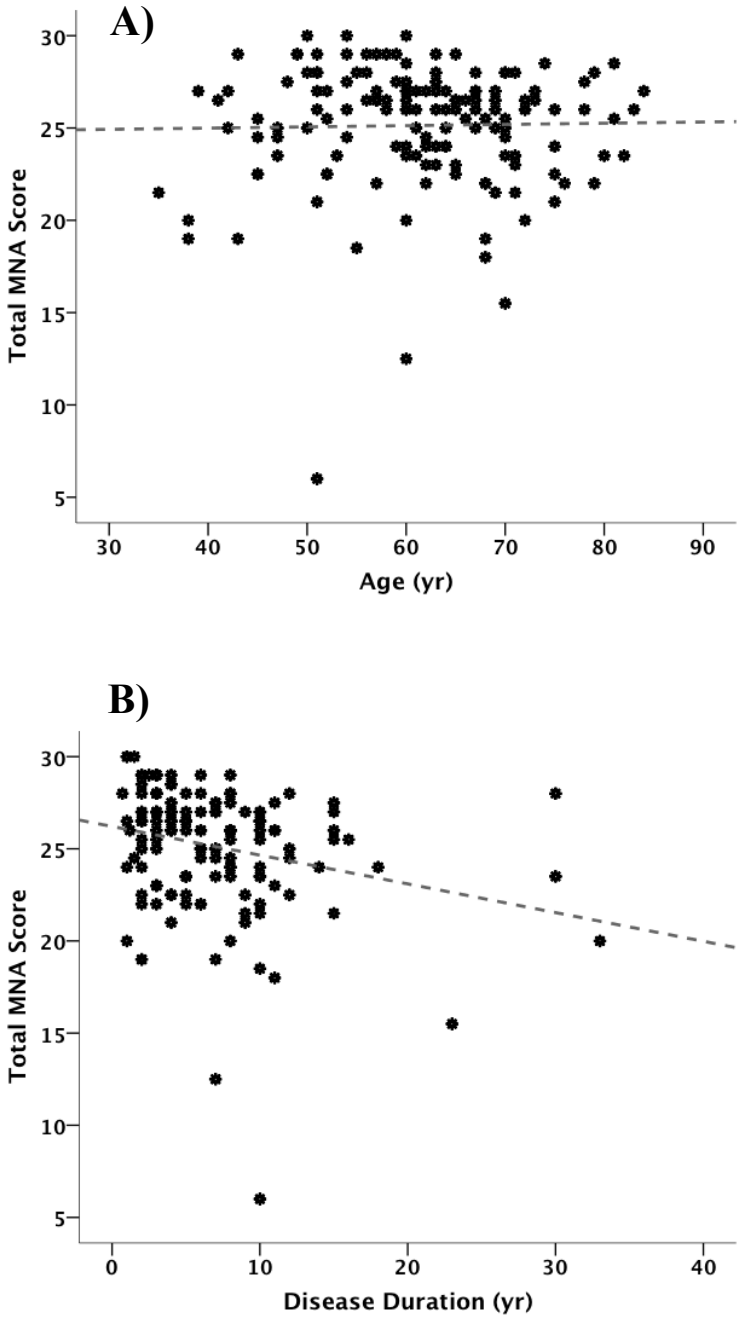


Figure 10. *Scatter plot of the correlation between total score of Mini Nutritional Assessment (MNA) and: A) patients' age (r=0.021, p=0.805); B) disease duration (r=-0.249, p=0.002) in Parkinson disease patients*

Table 11. *Multivariate regression models to determine the motor and non-motor factors independently related to total score of the MNA questionnaire (model 1) and having abnormal versus normal nutritional status (model 2) in recruited Parkinson disease (PD) patients (In both regression models, age at the time of diagnosis, sex, weight-adjusted levodopa dosage, the score of the each part of the UPDRS scale, total UPDRS score, Hoehn & Yahr stage, Schwab & England ADL score, anxiety, depression and fatigue scores were entered as the predictor list.)*

Model 1: **Linear regression** (Dependent variable: total MNA score)					
Significant Variables	**Unstandardized Coefficients**		**Standardized Coefficients**	***t***	***p*-value**
	B	SEM	Beta		
Gender	-1.53	0.50	-0.20	-3.03	0.003*
Weight-adjusted levodopa dosage	-0.09	0.03	-0.19	-2.82	0.006*
Depression score	-0.29	0.06	-0.35	-4.55	<0.001*
Total score of UPDRS	-0.06	0.02	-0.31	-3.90	<0.001*
Constant	30.15	0.50	-	59.87	<0.001*
Model 2: **Binary Logistic regression** (Dependent variable: abnormal vs. normal nutritional status)					
Significant Variables	**B**	**SEM**	**OR** (95% CI)	**Wald**	***p*-value**
Depression score	0.35	0.07	1.42 (1.24-1.64)	24.26	<0.001*
Hoehn & Yahr stage	0.87	0.32	2.38 (1.26-4.46)	7.23	0.007*
Constant	-4.98	0.97	-	26.33	<0.001*

SEM: standard error of mean, CI: confidence interval, OR: odds' ratio

* Statistically significant (p-value<0.05)

4.6 Quality of life in Parkinson's disease

Univariate associated factors and multivariate determinants of HRQoL in total IPD population (n=157) who were recruited from the Movement Disorders Clinic were assessed in *study VI*. Further analyses were performed to investigate the potential heterogeneity in the role of these factors and general pattern of HRQoL between different phenotypes of IPD patients.

4.6.1 Univariate correlates

Several baseline characteristics, motor severity and subtypes, and NMS significantly correlated with PDSI as a single indicator of HRQoL. Patients with lower tremor score [unadjusted coefficient=-0.26 (95% CI: -0.44–-0.08)], fall [unadjusted coefficient=12.15 (95% CI: 7.56-16.74)], freezing [unadjusted coefficient=13.33 (95% CI: 8.67–18.00)], more symmetric

disease [unadjusted coefficient=-18.91 (95% CI: -29.10–-8.72)], cognitive impairment [unadjusted coefficient=7.98 (95% CI: 2.82–13.14)], hallucinations [unadjusted coefficient=16.66 (95% CI: 9.68–23.63)], apathy [unadjusted coefficient=12.75 (95% CI: 8.12–17.39)], sleep disturbances [unadjusted coefficient=8.93 (95% CI: 4.09–13.77)], higher depression [unadjusted coefficient=2.47 (95% CI: 2.07–2.87)], anxiety [unadjusted coefficient=1.75 (95% CI: 1.36–2.14)] and fatigue [unadjusted coefficient=3.63 (95% CI: 2.47–4.79)] scores, and worse nutritional status [unadjusted coefficient=-2.41 (95% CI: -3.05–-1.77)] had worse HRQoL indicated by a higher PDSI.

4.6.2 Multivariate determinants

The tolerance statistics were all >0.40 and the VIF<2.5 demonstrating no serious problem with the collinearity issue in all multivariate regression models. As it is summarized in *Table 12*, anxiety [adjusted coefficient=0.51 (95% CI: 0.15–0.87)], depression [adjusted coefficient=1.11 (95% CI: 0.63–1.59)] and UPDRS-part II (ADL) [adjusted coefficient=0.90 (95% CI: 0.60–1.20)] scores were the significant independent determinants of PDSI after adjustment for sex, level of education, comorbidity score and PD duration as the baseline covariates.

Considerable differences were found in the determinants' list of each HRQoL domain. Female sex, higher depression score and more impaired ADL were significant predictors of worse HRQoL in "*mobility*" and "*social support*" domains (all adjusted coefficients>0 and $p<0.05$). "*Emotional well-being*" was significantly worse in IPD patients who were female [adjusted coefficient=7.18 (95% CI: 1.02–13.34)], scored higher for anxiety [adjusted coefficient=1.65 (95% CI: 0.98–2.31)] and depression [adjusted coefficient=1.99 (95% CI: 1.11–2.88)] and had less severe motor signs [adjusted coefficient=-0.53 (95% CI: -0.93–-0.12)]. More severe anxiety [adjusted coefficient=1.15 (95% CI: 0.20–2.10)], more impaired ADL [adjusted coefficient=0.85 (95% CI: 0.07–1.64)] and less severe motor signs [adjusted coefficient=-0.57 (95% CI: -1.15–0.01)] were the strongest determinants of "*stigma*". Higher number of comorbidities [adjusted coefficient=2.63 (95% CI: 0.02–5.24)] accompanied with a worse "*cognition*" dimension of the HRQoL and "*communication*" was mostly affected by depression [adjusted coefficient=1.33 (95% CI: 0.49–2.17)] and motor symptoms [adjusted coefficient=0.81 (95% CI: 0.29–1.33)] in IPD patients.

4.6.3 Structural equation model

As it is illustrated in *Figure 11*, the best SEM consisted of two major latent exogenous variables to characterize the global "*motor*" and "*non-motor*" components of PD, and the eight dimensions of the PDQ-39 questionnaire were indicated by an endogenous latent variable representing the general HRQoL. This model had 267 degrees of freedom and a Chi square value of 557 ($Chi^2/df=2.1$, $p<0.001$).

Table 12. *Multivariate linear regression model to find the baseline and clinical predictors of the Parkinson disease summary index (PDSI) as a single indicator for health-related quality of life (HRQoL) in Parkinson disease patients*

Independent Variables	Unstandardized Coefficients (95% CI)	Standardized Coefficients	*p*-value	Collinearity Statistics	
				Tolerance	VIF
Female Sex	5.30 (1.97 – 8.62)	0.16	0.002*	0.83	1.21
Disease Duration	-0.24 (-0.54 – 0.07)	-0.08	0.127	0.78	1.29
Comorbidity Score	1.33 (-0.15 – 2.81)	0.08	.079	0.97	1.03
Anxiety Score	0.51 (0.15 – 0.87)	0.17	.006*	0.59	1.70
Depression Score	1.11 (0.63 – 1.59)	0.32	<0.001*	0.45	2.21
MNA Total Score	-0.14 (-0.71 – 0.43)	-0.03	0.634	0.57	1.77
Fatigue Score	0.33 (-0.58 – 1.24)	0.04	0.48	0.67	1.50
UPDRS Score Part I-items 1, 2, 4	0.69 (-0.20 – 1.57)	0.08	0.127	0.71	1.41
Part II- ADL	0.90 (0.60 – 1.20)	0.43	<0.001*	0.41	2.42
Part III- Motor	-0.12 (-0.34 – 0.10)	-0.07	0.269	0.49	2.05
Constant	3.66 (-13.40 – 20.72)	-	.672	-	-

CI: confidence interval, VIF: variance inflation factor

* Statistically significant (p-value<0.05)

With RMSEA=0.08, NFI=0.74, CFI=0.84 and TLI=0.82, the model could explain 89% of the variance of total HRQoL. All standardized regression weights were statistically significant (p<0.05). Three direct correlations (between cognition and hallucination in the non-motor section, anxiety on "*emotional well-being*" dimension of HRQoL, "*social support*" and "*communication*" dimensions of HRQoL) were added in order to improve the model. In the entire study population, non-motor latent domain had a larger direct effect on HRQoL compared to that of the motor (SRW=0.69 vs. 0.32), while the motor domain showed an indirect effect mediated through the non-motor section as large as 0.49 resulting in the total effect of 0.81 from the motor domain on HRQoL. ADL (SRW=0.94), motor signs (SRW=0.70) and falling (SRW=0.70) were the strongest indicators of the motor latent variable.

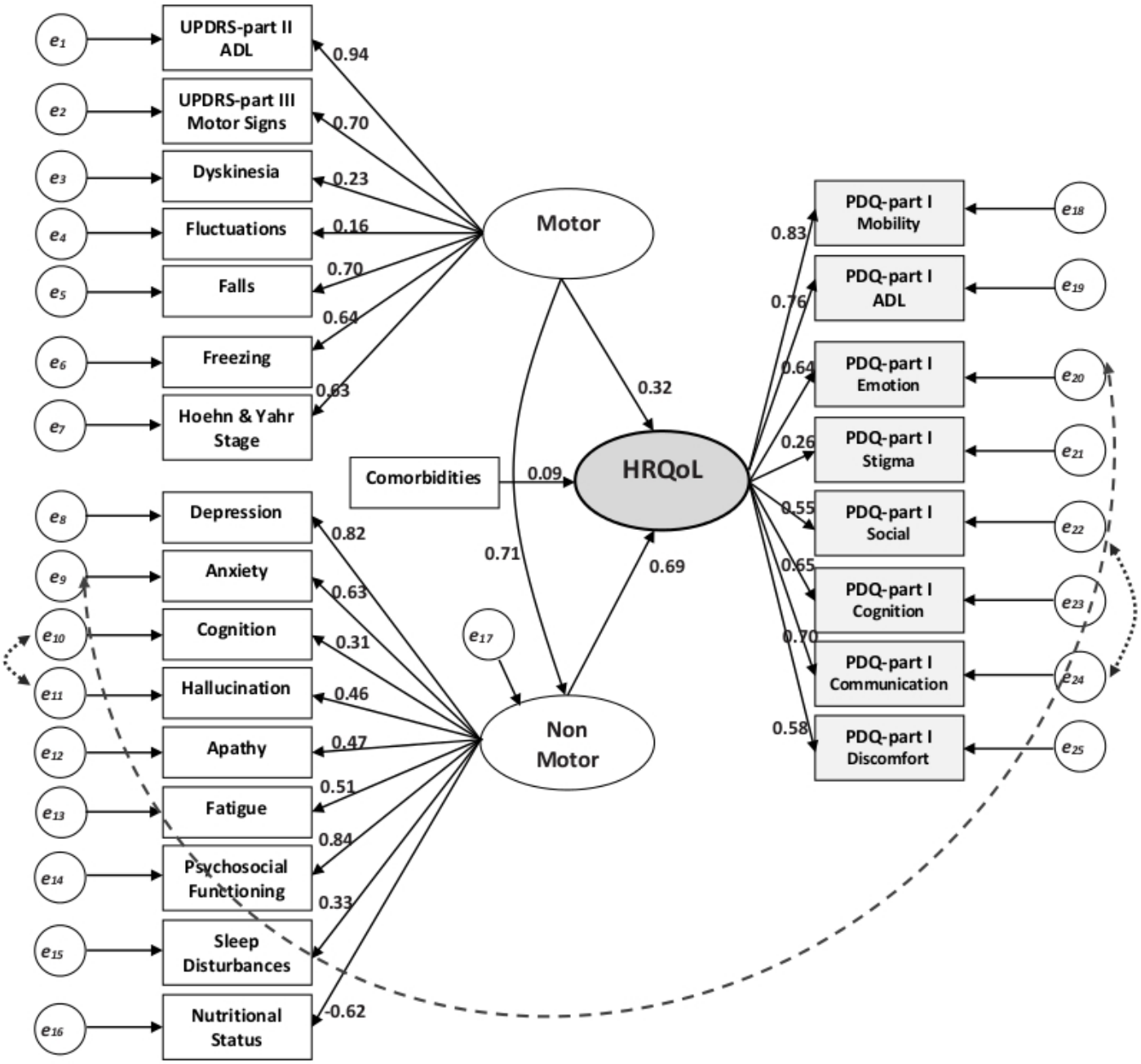


Figure 11. *Structural equation model for the factors affecting health-related quality of life (HRQoL) in patients with Parkinson disease [all standardized regression weights are statistically significant at p<0.001 except for the effect of comorbidities on HRQoL (p=0.045), the indication of motor domain on fluctuations (p=0.062) and dyskinesia (p=0.001), and the indication of HRQoL on stigma (p=0.001)]*

Psychosocial functioning (SRW=0.84), depression (SRW=0.82) and anxiety (SRW=0.63) were the most determinant factors for the non-motor latent domain to affect HRQoL. The same hypothetical SEM was re-structures in subgroups of PD with different phenotypes regarding onset-age, progression and dominant symptom. *Figure 12* illustrates the heatmap for the SRWs from the phenotype-specific SEMs. The intensity of colors represents the magnitude of each association in the SEM for each PD phenotype. The strength of the main associations and indicators of the latent variables were heterogeneously different for each phenotype.

Motor domain showed larger direct impact on HRQoL compared to non-motor section in younger-onset (SRW=0.61, $p<0.001$) and rapid-progression PD (SRW=0.57, $p<0.001$), whereas among typical-onset, slow-progression, tremor and non-tremor-dominant PD, non-motor domain had larger direct effect (all $p<0.05$). In patients with slow-progression PD, non-motor domain showed the largest direct effect (SRW=0.95, $p=0.005$) on HRQoL and all of the effects of motor domain was mediated through non-motor section. Comorbidity profile showed significant effect on HRQoL only among those with >50 years of age at the time of diagnosis (SRW=0.14, $p=0.007$) and non-tremor-dominant PD (SRW=0.13, $p=0.037$).

Obvious heterogeneities were also noted in the indicators profile of each phenotype. In younger-onset patients, depression was the strongest driver of the non-motor latent variable (SRW=0.91, $p=0.004$). Sleep disorder was a significant indicator for non-motor domain to affect HRQoL only among older-onset (SRW=0.33, $p=0.004$), slow-progression (SRW=0.32, $p=0.031$) and non-tremor (SRW=0.37, $p=0.008$) phenotypes. Opposite to the rapid-progression phenotype, fatigue was a significant indicator for non-motor domain among the slow-progression PD patients (SRW=0.49, $p=0.010$). In contrast to all other phenotypes, both dyskinesia (SRW=0.42, $p=0.012$) and fluctuations (SRW=0.33, $p=0.043$) showed significant contributions in the motor domain to affect HRQoL among the younger-onset patients. Regarding different indicators of HRQoL, "*cognition*" showed the highest SRW among the older-onset patients (0.72), whereas "*mobility*" had the largest SRW in younger-onset PD phenotype (0.90).

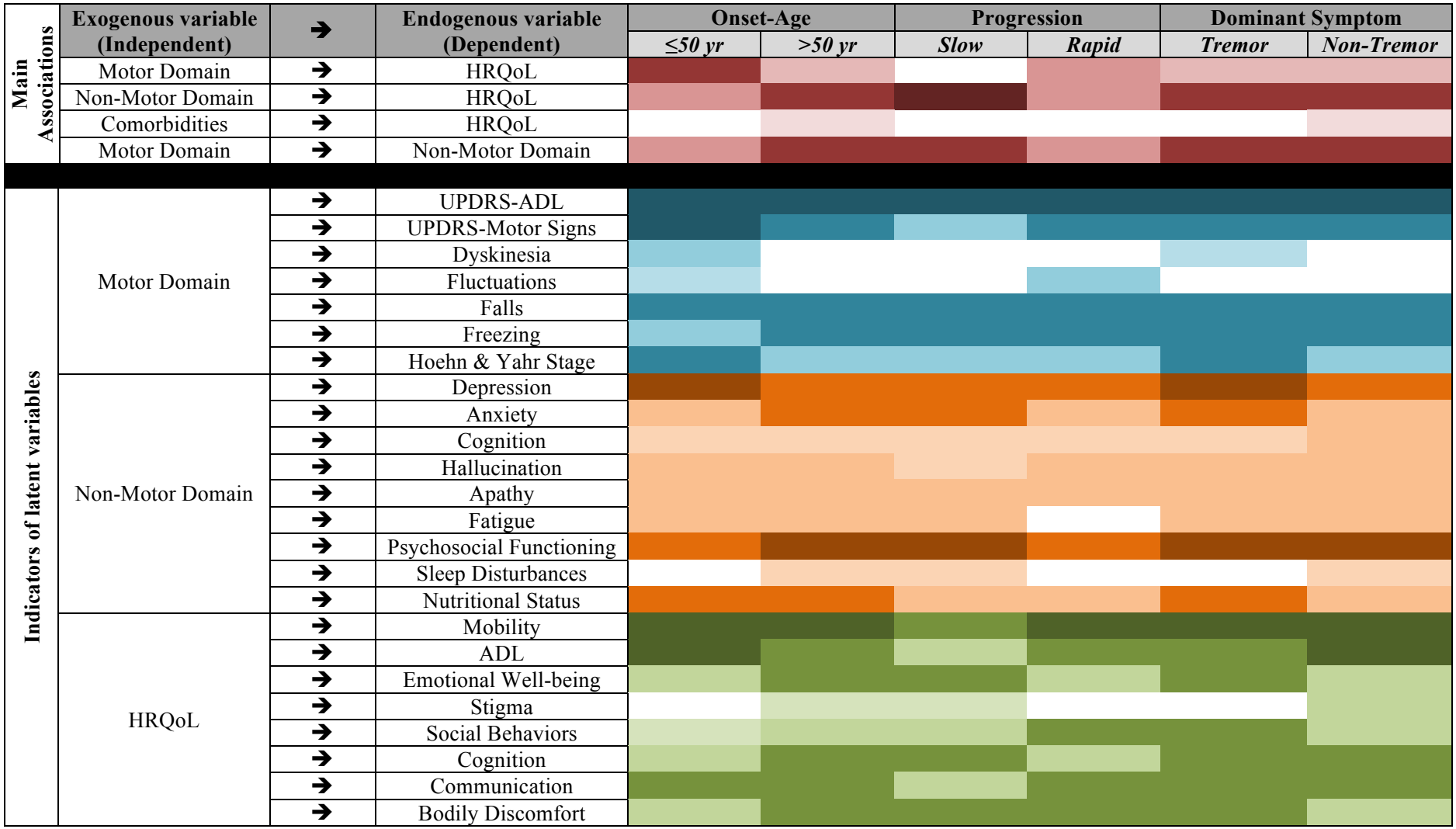


Figure 12. *Heatmap of the standardized direct regression weights (SRW) from the structural equation models (SEM) to evaluate factors affecting health-related quality of life (HRQoL) and the indicators of motor domain, non-motor domain and HRQoL in different phenotypes of Parkinson disease patients [the intensity of colors represents 0.2 unit (one quintile) increase in SRW for each section]*

5 DISCUSSION

5.1 Summary and interpretations of the main findings

5.1.1 Questionnaire validations

Through validation studies, we showed that the Persian-translated versions of the FSS [110], SCOPA-PS [112], MNA [113], PDQ-39 and PDQ-8 [115] were trans-culturally reliable and valid to assess fatigue, psychosocial functioning, nutritional status and HRQoL in Iranian PD patients, respectively (*Table 6*). These scales were also proved to be reliable and valid within different subgroups regarding age category, sex, educational level and PD severity. More specifically about the PDQs, we demonstrated that the composition of the items in the short-form version (PDQ-8) was appropriate enough to validly assess different aspects of HRQoL especially the mental and behavioral domains [115], which is in line with a previous report [129]. Literature review on other studies showed that the Cronbach's alpha coefficient of the PDQ-8 was between 0.72 and 0.88, which is lower than the long-form version (PDQ-39). Our reliability coefficient (0.74) is close to the Greek (0.72) [130], Italian (0.72) [131] and English version in Canadian (0.72) [132] and Singaporean (0.75) [133] PD populations while some other studies showed higher alpha coefficients for the reliability of the PDQ-8 [129, 134-136].

5.1.2 Novel screening instrument for parkinsonism

In *study II*, a new screening instrument was developed containing six items, three of which refer to the cardinal symptoms on "*stiffness & rigidity*", "*tremor & shaking*" and "*slower daily activity*" and three others namely "*troublesome buttoning*", "*troublesome arm swing*" and "*feet stuck to floor*" [88]. In line with previous studies [99, 107, 137], tremor had the highest diagnostic value as a single symptom to discriminate parkinsonism from healthy condition. Using the new concept of CUI to select the best screening symptoms, our new 6-item instrument showed the strongest diagnostic value to screen parkinsonism in comparison with the previously developed tools [88]. Our newly developed instrument showed the highest Youden's index (0.861) and specificity (96%), while, the WHO recommended questionnaires [102-103] had a higher sensitivity (95%) but lower specificity (60% and 72%). Our new instrument also showed the highest overall accuracy with an AUC of 0.977 compared to others including the SNES [99] (0.934), WHO modified instrument [102] (0.933), recommended index by *Daurte et al* [105] (0.947), *Setthawatcharawanich et al* [107] (0.950) and *Chan et al* [106] (0.968) to screen parkinsonism. Further subgroup analysis demonstrated that our new instrument remains valid for screening of parkinsonism within different age categories and severity of symptoms. In other words, it can accurately screen individuals suspicious of parkinsonism even with young age and mild symptoms during the early-stage of their disease.

5.1.3 Prevalence of parkinsonism and Parkinson's disease

Using our newly developed screening instrument in the first community-based doo-to-door neuroepidemiologic survey on parkinsonism in Tehran, Iran, the adjusted screening-detected prevalence rate was found to be 223/100,000 and 285/100,000 based on Tehran and "*WHO World Standard*" populations, respectively [42]. Both estimations could be considered as medium-to-high compared with other countries (*Table 2*). Previous surveys demonstrated that around 58-70% of the positively screened cases for parkinsonism actually have PD [5-6, 29, 138-140]. Accordingly, it could be expected that PD prevalence in Tehran urban population could be expected to range between 129-156/100,000 (standardized by Tehran population) or 165-199/100,000 (standardized by "*WHO World Standard Population*"). This rate is in between of the wide range of PD prevalence estimated for Caucasians populations (65-257/100,000) [37]. Focusing more on the Middle East where Iran is located, a higher PD prevalence is seen in Egypt, Tunisia and Turkey, Iran is in the middle range and Saudi Arabia has the lowest estimation (*Table 2*). There is another study to investigate PD prevalence in Persian ethnic group that has been done on the *Parsi* community (group of Persians who migrated from Iran to South Asia between the seventh and tenth centuries A.D.) in Bombay, India [32]. *Bharucha et al* showed that PD prevalence is higher among these Persians (192/100,000) who live in India compared to the highest rates reported for Indians themselves [141]. Interestingly, the prevalence rate of PD in *Parsi* population of India is much closer to our estimations from Iran. Nonetheless, not only ethnicity but also various environmental factors may play role to have such a varied prevalence features for PD. In China, a tenfold difference in PD prevalence has been shown from a nationwide survey covering different parts of the country highlighting the role of environmental factors as well [35]. In our study, prevalence of suspicious parkinsonism increased by advancing age and the overall male/female ratio was 1.62 [42], which is quite similar to one report from Norwegian PD population (1.58) [142].

5.1.4 Nutritional status in parkinsonian patients

Using the validated version of the MNA, similar proportion of both PD patients and controls (2.1% vs. 2%) were detected to be malnourished in *study IV* and the mean MNA score was not significantly different between the two groups [55]. In line with previous reports from the Chinese and Italian PD populations that have used MNA as well [60-61], close to a quarter of Iranian PD patients were found to be at risk of malnutrition. The unexpected low rate of severe malnutrition in all of these populations [55, 60-61] is believed to mainly stem from the source of patient selection. All patients were recruited from outpatient clinics where disabled in-hospitalized cases were not included and majority of the samples were in the mild-to-moderate stages of PD. In the Chinese PD population, malnutrition was observed only in 1.7% and such a low rate was attributed to race, age, Hoehn and Yahr stage and disease duration [60]. In

another Italian survey, underweightness was also reported to be uncommon in PD patients and the authors concluded that the general overweightness in industrialized countries and the modern antiparkinson therapies might be possible reasons [143]. Specifically in our study, another issue might have also contributed to the rather low and similar prevalence rate of malnutrition compared to the controls, which is related to the cultural behaviors and values in Iranian society. The family members, spouses and caregivers of the elderly patients usually pay more attention to elderly patients including providing appropriate nutritious diet for them when they are sick. The patients with mild to moderate stages of PD mostly live with their own families at their homes where they can benefit from these extra supports. Otherwise, it seems that elderly PD patients who are living alone may face difficulties in food preparation and appropriate nutrition on their own [55]. Regardless of all of these interpretations, it is important to bear in mind that almost one third of Iranian PD population in *study IV* were either at risk of malnutrition or malnourished, the fact which should be considered for a more efficient management strategy.

Among the anthropometric measurements, CC was in average smaller in PD patients compared to the controls [55], which might be due to the excess adiposity and depletion of lean body mass in PD [144]. BMI has been typically used as another indicator for nutritional status in PD population. However, different cut-off values have been applied to define malnutrition based on BMI ranging from 18.6 kg/m^2 [70] to 22 kg/m^2 [67] in different reports. One longitudinal study showed that 15.6% of PD patients versus 5.1% of the controls developed malnutrition, which was defined as BMI<22 kg/m^2 [67]. Using a lower cut-off point as BMI<20 kg/m^2, prevalence of malnutrition was shown to be 19.5% and 9.3% in urban or rural PD populations, respectively [145]. In our study, 11.2% of the PD patients had BMI<21 kg/m^2, which was close to that of the matched controls (10.3%) [55]. A recent meta-analysis showed that PD patients had a significantly lower BMI than controls, and patients with Hoehn and Yahr stage 3 had even lower BMI compared to those at stage 2 [146]. This can explain why we did not find any difference in the average BMI values between the controls and PD patients who were mostly in stage 2 or less in our study [55].

Results from *study V* demonstrated that several demographics, motor and non-motor features associated with nutritional status in PD patients (*Table 3*). PD patients with nutritional insufficiency had more severe symptoms in all parts of the UPDRS scale namely motor, non-motor, ADL and complications [73]. Both dyskinesia and wearing-off phenomenon were more common among PD patients with abnormal nutritional status [73]. This finding is aligned with another study that reported dyskinesia as an important determinant of anthropometric measurements in a group of PD patients with more advanced stage than our study population [70]. We observed more severe depression and anxiety in PD patients with nutritional problems, which is quite in line with several previous studies on different PD populations [60, 69]. Our study is the first to show a strong univariate association between fatigue and

nutritional status in PD patients, however, no causal inference were made since fatigue and exhaustion could potentially be considered as both cause and consequence of malnutrition [73]. Following multivariate adjustment, female sex, higher weight-adjusted daily levodopa dosage, more severe disability (higher total UPDRS score, more advanced Hoehn and Yahr stage) and more severe depression independently predicted lower MNA score representing a higher risk of nutritional insufficiency in people with PD [73]. Female PD patients had significantly worse nutritional status even after statistical adjustment for other covariates, which is in line with previously published reports indicating female sex as a risk factor for malnutrition in the elderly based on the total MNA score [147], or PD patients using anthropometric indices [66, 71]. Similar to some previous reports [69, 71, 148], we also could not find any association between nutritional status and daily dosage of levodopa. Nevertheless, when the cumulative daily dosage of levodopa was adjusted for body weight (*mg per kg body weight*), it significantly correlated with the total MNA score in ours [73], *Sheard et al*'s [69] and *Barichella et al*'s [68] studies. Interestingly, while no association was found between patient's age and total MNA score, longer disease duration accompanied with worse nutritional status in PD patients.

In *study V*, we also showed that nutritional status strongly affected HRQoL. PD patients who were malnourished or at risk of malnutrition had poorer life quality in all domains of PDQ-39 except for stigma. To our knowledge, our study was one of the few that directly assess the relationship between nutritional status and HRQoL using MNA and PDQ-39 in PD patients. Similar association has been previously shown in another elderly population from rehabilitation centers [52].

5.1.5 Quality of life in Parkinson's disease

In *study VI*, female sex, lower level of education, higher number of comorbid conditions and longer duration of disease were demographic characteristics that adversely affected HRQoL. Through univariate analysis, several motor and non-motor features were found to significantly influence HRQoL in our study population. PD patients with more severe motor disabilities (both responsive and non-responsive to levodopa), higher dependency in their daily lives, lower tremor score, more symmetric subtype, higher freezing, fall and more severe gait disturbances experienced poorer HRQoL. Cognitive impairment, hallucination, apathy, sleep disturbances, anxiety, depression and fatigue were detected as the non-motor drivers of HRQoL. Interestingly, worse nutritional status and less psychosocial activity also accompanied with poorer HRQoL in people with PD as shown in *study VI*. Following multivariate analysis, motor symptoms affecting activities of daily life, depression, anxiety and female sex were found to be the strongest independent determinants of HRQoL in Iranian PD population, respectively. In domain-specific analyses, PD patients with a higher number of comorbidities had in average a 2.6 poorer score in cognitive dimension. Mental and behavioral symptoms

such as apathy, cognitive impairment and hallucination adversely affected cognition and bodily discomfort dimensions of the HRQoL in parkinsonian patients. Noteworthy, less severe motor signs (UPDRS-Part III) associated with worse emotional-well being and stigma scores showing that these domains are mainly affected at the early stages of PD and coping mechanisms during the next years could improve these aspects of HRQoL in parkinsonian patients.

In line with our findings, non-motor symptoms, higher motor severity shown by Hoehn and Yahr score and UPDRS-Part III, motor complications, female sex, longer disease duration and being single or divorced have been shown to negatively affect the overall HRQoL in a population of Chinese PD patients which is quite similar to ours regarding the average PDSI (21.2 vs. 21.7) [83]. Similarly, they have also found that NMSs are the main determinants of HRQoL in all dimensions. However, they have used the non-motor symptoms scale of Parkinson's disease (NMSS) as a general instrument for NMSs [83], while we have evaluated them with more specific tools and shown that depression and anxiety are probably the main non-motor drivers of HRQoL in PD patients. Several other studies have also concluded that NMSs were the main determinant factors for HRQoL [74, 79-81, 83, 149-150], and some have specified depression and anxiety as the most important responsible factors for poor HRQoL in parkinsonian patients [150-153]. PD severity and disability indicators such as ADL and level of dependency have been commonly shown to be another important driver of worse HRQoL in PD patients [76, 154], which is consistent with the independent role of UPDRS-ADL score found in our investigation. Female sex as a risk factor for poorer HRQoL in PD has been previously shown [83, 155-157], yet with some controversial findings in some other studies [79, 82, 158]. Although a worse life quality in women with a chronic disease can be generally attributed to the rather higher burden of depression and anxiety, our study demonstrated that female sex remained an independent risk factor for poor HRQoL in PD even after adjustment for psychiatric symptoms and their severities.

Using the concept of structural modeling, we demonstrated that the best hypothesized structural causal model in the whole PD population consisted of motor, non-motor and comorbidity components, which could explain up to 89% of the variance in HRQoL indicator. UPDRS-Part II, UPDRS-Part III and falling were found to be the most important indicators for the global motor component, while depression and psychosocial functioning were the strongest indicators for the global non-motor component. As it is illustrated in *Figure 11*, anxiety had a direct and strong effect on emotional well-being domain of HRQoL in PD patients and seemed to be its main determinant. Our investigation revealed that nutritional status and fatigue played a key independent role in the non-motor component to affect HRQoL in PD. Other motor and gait complications such as dyskinesia, fluctuations and freezing were all independent indicators of the global motor component in the pathway to affect HRQoL. However, a substantial proportion of the overall contribution of motor symptoms in HRQoL was mediated through the non-motor component. We found outstanding heterogeneities in the structural model of

HRQoL in different PD phenotypes (*Figure 12*). Interestingly, the comorbidity component was shown to be an important determinant of HRQoL only among those with either older-onset or non-tremor-dominant PD. Among the patients with rapid progression PD, a chronicity symptom such as fatigue was not a significant indicator of the non-motor section, while the motor component had a larger direct effect on HRQoL. In contrast, the impact of motor component on HRQoL was mostly mediated through the non-motor component, as the main driver of HRQoL in slow-progressive PD. Contribution of global motor component in HRQoL was remarkably different between the younger-onset and older-onset PD patients such that the importance of direct effects of motor symptoms on HRQoL was three-time larger in younger-onset patients. As an important marker of HRQoL, sleep disorders showed significant contribution in the global non-motor component only among the older-onset, slow-progression and non-tremor-dominant phenotypes.

So far, a few studies have used SEM to comprehensively evaluate the pattern of HRQoL in PD [159-160]. In one study, depression had the largest contribution in HRQoL followed by axial motor, gastrointestinal, and urinary symptoms, and psychosocial well-being showed a stronger impact compared to physical functioning [159]. According to their recommended SEM, other symptoms such as pain, psychiatric complications, motor symptoms, autonomic dysfunction, motor complications and daytime sleepiness, indirectly affect HRQoL via psychosocial well-being and ADL [159]. Using path analysis in another study, direct contribution of self care-related factors such as functional disability and falls has been shown in HRQoL of people with PD [160]. More recently, another SEM has been proposed in which depression and pain were the main factors that could directly affect HRQoL in PD [161]. Even though different structural models have been hypothesized, our findings on the general model are aligned with them. In all SEMs, either functional disabilities or psychiatric well-being such as depression have been pointed out as the most consistent factors associated with poorer HRQoL in PD patients. Nevertheless, there are some differences in the list of variables that have been used to create these models and none of them have compared the model between different PD phenotypes. Some previous studies have compared HRQoL between younger-onset and older-onset PD patients using regression analysis where more severe depression and more impaired emotional domain of HRQoL have been shown in younger-onset PD patients [157, 162]. In line with these findings, our study also demonstrated a more prominent role for depression in the global non-motor component to affect HRQoL among PD patients with earlier age of onset.

5.2 Methodological considerations

5.2.1 Limitations

We acknowledge the limitations of our project that are categorized as the following topics:

- *Study design:* Cross-sectional design is the major obstacle for interpretation on causality between the hypothetical exposures and outcomes. Therefore, we have mostly concluded on associations and/or correlations. In *study V*, no causal relationship could be concluded between nutritional status and its determinants since the outcome of interest (malnutrition) and associated factors were all assessed at the same time point. Therefore, it is not clear whether malnutrition is the cause or the effect or in other words, "*the chicken or the egg*" [163]. In a cross-sectional study, the relationship between PD symptoms and nutritional status remains reciprocal. While poor management of PD symptoms can increase the risk of malnutrition, poor dietary status can itself result in worse symptoms [73].

- *Generalizability:* We used data collected from an outpatient Movement Disorder Clinic in *study I*, *study II*, *study IV*, *study V* and *study VI*. In this setting, fewer patients with advanced stages of PD are usually recruited leading to a potential selection bias that might restrict generalizability of the findings mainly to mild-to-moderate PD patients. In *study III*, one should consider that though Persians are the major ethnic group, Tehran population is a mixture of different ethnicities consisting of Persian, Azeri, Kurdish and even immigrant sub-populations namely Afghan and Iraqi. As a result, our findings on the prevalence of parkinsonism are more appropriately generalized to Iranian urban population as a geographic entity rather than Persian ethnic group [42].

- *Internal* validity: Due to limited resources, lack of a confirmatory assessment in a phase II study by well-trained neurologists is the major weakness of *study III*. Even though the screening instrument showed quite high diagnostic value, the positively screened individuals for parkinsonism in *study III* still need to be re-evaluated by expert neurologists for final diagnosis of parkinsonism following physical examination. With respect to this limitation, all prevalence features in *study III* were expressed as screening-detected suspicious parkinsonism. In *study IV* and *study V*, no blood sample was collected to quantify serum indicators of malnutrition such as albumin. Nonetheless, MNA is now considered as an innovative clinical instrument that provides valid information on several aspects of nutritional status containing four anthropometric measurements with no need for further blood tests and other clinical evaluations [55]. MNA has been approved to assess nutritional status mainly among the elderly people aged >65 *yrs*. Therefore, our data from younger patients might not be as valid as those from the older ones resulting in an information bias. However, in the validation study we showed that MNA could be a valid instrument for younger individuals as well [113]. In addition, two other studies have used MNA to assess nutritional status in participants with approximately the same range of age as ours [60, 164]. In *study VI*, data on some

other important PD-related features have been missed such as pain and RBD, which might potentially affect HRQoL. Data validity could have been improved by using more objective methods like polysomnography for sleep disturbances, blood pressure measurement to detect orthostatic hypotension and a full neuropsychological assessment for cognitive impairments. Nonetheless, we had some resource, instrumental and time restrictions to perform all these measurements that could be addressed for future studies on determinants of HRQoL.

- *Confounders:* Although an age- and sex-matched control group was recruited for comparisons of nutritional status with PD patients in study *IV*, the case group had significantly higher educational level considering as a proxy for better socioeconomic status that could have confounded nutritional comparisons. This confounding effect might have compensated the potential influence of PD on nutritional status compared to the normal condition. This might have probably stemmed from the source of control selection. While controls were recruited from educational hospitals with free services (patients' relatives), the cases were selected from an outpatient private clinic, which might have resulted in inconsistency of socioeconomical status. Nevertheless, multivariate analysis showed no significant difference in the average MNA score between PD patients and the controls even after adjustment for the imbalance in educational level [55].

5.2.2. Strengths

The strengths of our project are as follows:

- *Comprehensive database:* In *study V* and *study VI*, a broad list of variables including demographics, comorbidity profile, motor and non-motor symptoms, fatigue, full UPDRS, nutritional status and HRQoL was evaluated, which has enabled us to consider numerous interactions, look for independent determinants and increase the reliability and validity of our findings. In *study VI* and in addition to the broad list of motor and non-motor features, comorbidity profile and nutritional status were also included in our analysis, whereas these two important determinants have been mostly ignored in previous studies on HRQoL in PD.

- *Large sample size and sampling method:* A large number of inhabitants (n=19,500) were recruited in the community-based door-to-door study through a well-designed multistage sampling that covered the whole urban area of Tehran. Consequently, the high statistical power and reliable representativeness of the samples have increased the validity of our findings in *study III*. In other studies where data were collected from the Movement Disorder Clinic, the recruited number of PD patients was

between 110 and 157, which is considered approximately high compared to the other similar studies on each topic.

- *Matched control group*: In *study IV*, an age- and sex-matched control group was used from the same community with similar socio-economic background to compare the prevalence of malnutrition with that of the PD group. To the best of our knowledge, our study is one of the few to recruit such a matched control group, which has led to a more valid interpretation on the magnitude of malnutrition in people with PD.

- *Sophisticated statistical methods:* In *study II,* we used the new statistical concept of CUI introduced by *Mitchell* [126, 165] to improve the interpretation of screening performance considering not only the diagnostic indices but also the occurrence of that symptom [165]. This simple approach resulted in selection of the most valid items, which globally demonstrated the best performance to screen parkinsonism. In addition to the multivariate regression model, which is the most common method that has been used to find determinant factors of HRQoL in PD [76], we also applied SEM in *study VI*. With respect to statistical considerations, SEMs are stronger models due to the ability of complex linkage between different components through simultaneous regression equations, and taking into account inter-relationships between predictor variables and observational errors from measurement of latent variables [166], here motor and non-motor components.

- *Fair comparison:* In *study II* where we attempted to compare different screening instruments, a comprehensive questionnaire was made through merging all previously developed tools consisting of 25 unique symptoms. Therefore, we were able to implement discriminant performance of all questionnaires on the same original database as our own new 6-item instrument was developed from. To the best of our knowledge, it was the first time to perform such a fair comparison between several screening tools for parkinsonism.

6 CONCLUSIONS

6.1 General conclusion

Using our novel 6-item screening instrument with high diagnostic accuracy, we showed a medium-to-high prevalence rate for suspicious parkinsonism in Iranian population living in the urban area of Tehran, Iran. With respect to some general aspects of life in PD, almost a similar nutritional status was found in mild-to-moderate PD patients and age- and sex-matched controls from the same community. Nevertheless, approximately one third of the PD population were either malnourished or at risk of malnutrition. Duration of PD, severity of motor symptoms, depression, anxiety and fatigue associated with nutritional status in people with PD. Different aspects of HRQoL were affected by nutritional status in PD patients, especially the emotional well-being and mobility domains. Motor symptoms affecting ADL, depression, anxiety and female sex were found to be the strongest independent determinants of HRQoL in Iranian PD population. Clear heterogeneities were demonstrated in the structural model to explain the pattern of HRQoL consisting of the list of determinants, contribution of motor and non-motor components and the projection of different domains of HRQoL in PD patients with different phenotypes regarding onset-age, progression rate and dominant features.

6.2 Specific conclusions

- *Study I:* The Persian version of the short-form PDQ (PDQ-8) is a reliable and valid instrument to assess HRQoL in Iranian PD population. Although the reliability coefficient of the PDQ-8 was lower than that of the long-form version (PDQ-39), it is still a valid tool to assess different domains of HRQoL especially the mental, emotional and behavioral aspects. Single items of the PDQ-8 were not necessarily those with the highest internal consistency within the corresponding components of the original PDQ-39, nevertheless, they entirely showed acceptable psychometric properties with no need for the replacement of any item.

- *Study II:* Using the concept of CUI to select the best items, we developed a valid and reliable new screening questionnaire for parkinsonism. This new 6-item instrument was shown to have superior diagnostic values compared to the previously developed questionnaires for screening of parkinsonian in community-based surveys. This short questionnaire consists of six items that could be easily administered by healthcare professionals in different age groups for screening of parkinsonian patients with even early-stage of the disease.

- *Study III:* Our estimation for the prevalence rate of parkinsonism is closer to the reports from some European and Eastern Mediterranean countries, higher than prevalence rates from Eastern Asian and African populations and lower than Australia. In general, a prevalence rate of >200/100,000 for parkinsonism in the urban area of Tehran, Iran is considered as medium-to-high. This prevalence rate has been estimated for a huge metropolitan with potentially high risk of exposure to pollutants, and other risk factors of urbanization.

- *Study IV:* Although similar nutritional status was found in mild-to-moderate PD patients and healthy controls, approximately one third of them were either at risk of malnutrition or malnourished. It seems that eating problems and nutritional insufficiencies are more prevalent during the advanced stages of PD and among hospitalized severe cases.

- *Study V:* Several non-motor features such as depression, anxiety and fatigue were related to nutritional status in PD patients as well as indicators of disease severity and level of morbidity. Regardless of patients' age, longer disease duration determined worse nutritional status. Different aspects of the HRQoL namely mobility, ADL, emotional well-being, social support, cognition, communication and bodily discomfort closely associated with patients' nutritional score.

- *Study VI:* In general, ADL, depression, anxiety, and female sex were found to be the strongest determinants of HRQoL in Iranian PD patients using multivariate analysis. A comprehensive structural model has been also conceptualized for better understanding of HRQoL in PD. This model clarified the role of global motor and non-motor components and their most important indicators to affect HRQoL in addition to the comorbidity burden as the main drivers. Clear heterogeneous patterns were observed in patients with different phenotypes, which need to be taken into account for future interventions to improve HRQoL in people with PD. Based on our findings, more attention should be paid on the emotional well-being and stigma domain of HRQoL in PD patients at the beginning of their diagnosis. PD patients with younger-onset, older-onset, slow-progression, rapid-progression, motor-dominant, and non-motor-dominant phenotype have noticeably different causal pathways and determinants for HRQoL.

7 RELEVANCE AND IMPLICATIONS

Our findings have the following direct and indirect clinical and/or research relevance, some of which have been already implied and the others have potential implication:

- *Study I:* In routine clinical practice with limited time, PDQ-8 is a practical and informative instrument that could be administered both either the clinicians, caregivers or PD patients themselves. Trans-cultural validation of the PDQ provides a unique opportunity to use this instrument as an international scale to measure improvements and/or changes in HRQoL as an important healthcare outcome in multi-center studies on PD populations including international clinical trials. Other than the PDQs, we validated the Persian-translated version of three other scales in people with PD namely FSS, SCOPA-PS and MNA. So far, three different study groups have contacted us for permission to use these validated Persian-translated scales in their researches on Iranian PD patients.

- *Study II:* Our new screening instrument is a useful tool to estimate the prevalence of cases suspicious of parkinsonism, which can be applied in future neuroepidemiologic studies especially in poor-resource settings. We already used this instrument in *study III* in order to screen individuals with parkinsonism and estimate its prevalence rate.

- *Study III:* Our study was the first attempt to estimate the prevalence of suspicious parkinsonism in Iranian population. These findings are great sources for healthcare policymakers in having evidence-based knowledge about the burden of parkinsonism. It is worth noting that our estimation on the probable prevalence of parkinsonism and PD in Iran has been already used as valid data source for the section of neurodegenerative disorders of the "*Global Burden of Disease (GBD) Study 2013*" project, the report which has been recently published as the global map of all human diseases [167].

- *Study IV:* Regarding the prevalence rate of nutritional insufficiency among PD patients with even mild-to-moderate severity, it is reasonable to recommend clinicians screening their patients in any stage for malnutrition through longitudinal monitoring. Appropriate brief assessment tools such as the MNA together with anthropometric measurements can be used for this purpose. Educating patients and their caregivers about nutritional issues and recommending necessary and evidence-based dietary interventions can be considered in multidisciplinary work-up of PD patients to prevent and/or handle malnutrition. Findings from *study IV* on the

prevalence of malnutrition in PD patients was released as relevant scientific news in simple language to be used by the PD patients' communities and their relatives as well as other audiences who might be interested in this topic. The news was published by the *IOS Press* on *11 September 2014* and is accessible through the cited electronic link [168].

- *Study V:* Our study was the first investigation looking for a better understanding of nutritional status among Iranian PD patients. Assessment of nutritional status should be considered in routine clinical practice of PD patients looking for risk of malnutrition and its negative effects on daily quality of life especially among those with more severe motor and non-motor features. More specifically, PD patients with more severe depressive symptoms, severe anxiety, severe fatigue, more severe disability with higher Hoehn and Yahr stage who are under a higher weight-adjusted levodopa dose are more likely to develop malnutrition and may benefit more from nutritional screening. Our findings raised further hypothesis whether the individuals with insufficient nutrient intake in the past were more likely to present a more severe course of PD, or if the presence of more severe PD symptoms can hinder the capability and/or willingness to engage in appropriate nutritious meal preparation and dietary behaviors.

- *Study VI:* As one of the first studies so far, we have deeply investigated heterogeneity in the pattern of HRQoL and the complex interactions between several various determinants in PD patients with different phenotypes. Our findings showed outstanding heterogeneities in the pattern and determinants of HRQoL between different PD phenotypes. These factors should be considered during the assessments and developing personalized interventions to improve HRQOL in PD patients with different phenotypes or prominent features. In other words, each person with PD must be evaluated for his/her more dominant phenotypic features, and thereafter a personalized approach should be planned for further evidence-based assessments and interventions according to the heterogenic findings for each phenotype, some of which have been presented by our project.

8 FUTURE DIRECTIONS

Based on our findings, the following specific directions and/or recommendations are proposed for future research on this topic:

1) To further investigate the performance of the screening instrument for discrimination between PD versus APs such as MSA, PSP, CBD drug-induced parkinsonism, vascular parkinsonism and ET, studies with larger sample size of different APs are recommended.

2) The rather medium-to-high prevalence rate of parkinsonism in Tehran, Iran needs to be further investigated for underlying reasons. Moreover, national comparisons with rural areas and between different Iranian ethnic groups are helpful to enlighten the neuroepidemiologic picture of parkinsonism as well as contribution of genetic and environmental factors in the incidence of parkinsonian syndrome.

3) Longitudinal studies with appropriate follow-up examinations of PD patients in different stages including severe cases with advanced symptoms are needed to provide a more complete and accurate picture of the nutritional status in PD. Afterwards, valid causal relationships can be inferred to find modifiable exposures for future interventions. Clinical trials are warranted to investigate the effects of nutritional interventions on prognosis and HRQoL in PD patients.

4) Future studies to design, implement and assess the effects of multi-domain personalized interventions for each PD patients according to his/her dominant phenotype are highly demanded. The intervention should be designed individually targeting multiple domains namely motor symptoms and complications, psychiatric features, sleep disorders, autonomic disturbances, other NMSs, nutritional status and comorbidity profile.

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10 REFERENCES

1. Jankovic J: Parkinson's disease: clinical features and diagnosis. *Journal of neurology, neurosurgery, and psychiatry* 2008, 79(4):368-376.
2. Hughes AJ, Daniel SE, Kilford L, Lees AJ: Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of neurology, neurosurgery, and psychiatry* 1992, 55(3):181-184.
3. Berg D, Postuma RB, Bloem B, Chan P, Dubois B, Gasser T, Goetz CG, Halliday GM, Hardy J, Lang AE *et al*: Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2014, 29(4):454-462.
4. Todorova A, Jenner P, Ray Chaudhuri K: Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected. *Practical neurology* 2014, 14(5):310-322.
5. Bergareche A, De La Puente E, Lopez de Munain A, Sarasqueta C, de Arce A, Poza JJ, Marti-Masso JF: Prevalence of Parkinson's disease and other types of Parkinsonism. A door-to-door survey in Bidasoa, Spain. *Journal of neurology* 2004, 251(3):340-345.
6. Benito-Leon J, Bermejo-Pareja F, Rodriguez J, Molina JA, Gabriel R, Morales JM: Prevalence of PD and other types of parkinsonism in three elderly populations of central Spain. *Movement disorders : official journal of the Movement Disorder Society* 2003, 18(3):267-274.
7. Schapira AH: Etiology of Parkinson's disease. *Neurology* 2006, 66(10 Suppl 4):S10-23.
8. Tan EK, Reichmann H: Causes of Parkinson's disease: genetics, environment and pathogenesis. In: *Parkinson's disease.* Edited by Schapira AHV, First edn. New York, United States: Oxford University Press; 2011: 5-16.
9. Samii A, Nutt JG, Ransom BR: Parkinson's disease. *Lancet* 2004, 363(9423):1783-1793.
10. Langston JW, Ballard P, Tetrud JW, Irwin I: Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983, 219(4587):979-980.
11. Harris MA, Shen H, Marion SA, Tsui JK, Teschke K: Head injuries and Parkinson's disease in a case-control study. *Occupational and environmental medicine* 2013, 70(12):839-844.
12. Dauer W, Przedborski S: Parkinson's disease: mechanisms and models. *Neuron* 2003, 39(6):889-909.
13. Jellinger KA: Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. *Movement disorders : official journal of the Movement Disorder Society* 2012, 27(1):8-30.
14. Braak H, de Vos RA, Bohl J, Del Tredici K: Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neuroscience letters* 2006, 396(1):67-72.

15. Hawkes CH, Del Tredici K, Braak H: Parkinson's disease: the dual hit theory revisited. *Annals of the New York Academy of Sciences* 2009, 1170:615-622.

16. Goldman JG, Postuma R: Premotor and nonmotor features of Parkinson's disease. *Current opinion in neurology* 2014, 27(4):434-441.

17. Recasens A, Dehay B: Alpha-synuclein spreading in Parkinson's disease. *Frontiers in neuroanatomy* 2014, 8:159.

18. Brundin P, Li JY, Holton JL, Lindvall O, Revesz T: Research in motion: the enigma of Parkinson's disease pathology spread. *Nature reviews Neuroscience* 2008, 9(10):741-745.

19. Fereshtehnejad SM, Rios Romenets S, Anang J, Latreille V, Gagnon JF, Postuma R: New Clinical subtypes of Parkinson's disease and longitudinal disease progression: A prospective cohort comparison with other phenotypes. *JAMA Neurol* 2015:[In Press].

20. Ishihara LS, Cheesbrough A, Brayne C, Schrag A: Estimated life expectancy of Parkinson's patients compared with the UK population. *Journal of neurology, neurosurgery, and psychiatry* 2007, 78(12):1304-1309.

21. Hobson P, Meara J, Ishihara-Paul L: The estimated life expectancy in a community cohort of Parkinson's disease patients with and without dementia, compared with the UK population. *Journal of neurology, neurosurgery, and psychiatry* 2010, 81(10):1093-1098.

22. Ossig C, Reichmann H: Treatment of Parkinson's disease in the advanced stage. *Journal of neural transmission* 2013, 120(4):523-529.

23. Richard IH, McDermott MP, Kurlan R, Lyness JM, Como PG, Pearson N, Factor SA, Juncos J, Serrano Ramos C, Brodsky M *et al*: A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. *Neurology* 2012, 78(16):1229-1236.

24. Valentino RM, Foldvary-Schaefer N: Modafinil in the treatment of excessive daytime sleepiness. *Cleveland Clinic journal of medicine* 2007, 74(8):561-566, 568-571.

25. Fereshtehnejad SM, Lokk J: Active aging for individuals with Parkinson's disease: definitions, literature review, and models. *Parkinson's disease* 2014, 2014:739718.

26. Lökk J, Fereshtehnejad SM: Managing palliative care in Parkinson's disease from diagnosis to end-stage disease: what the clinician should know. *Neurodegenerative Disease Management* 2013, 3(2):169-183.

27. Morgante L, Nicoletti A, Epifanio A, Contrafatto D, Savica R, Lanzafame S, Musolino R, La Spina P, Bonuccelli U, Marconi R *et al*: Prevalence of Parkinson's disease and other types of parkinsonism in the Aeolian Archipelago, Sicily. *Parkinsonism Relat Disord* 2008, 14(7):572-575.

28. Hobson P, Gallacher J, Meara J: Cross-sectional survey of Parkinson's disease and parkinsonism in a rural area of the United Kingdom. *Movement disorders : official journal of the Movement Disorder Society* 2005, 20(8):995-998.

29. El-Tallawy HN, Farghaly WM, Shehata GA, Rageh TA, Hakeem NM, Hamed MA, Badry R: Prevalence of Parkinson's disease and other types of Parkinsonism in Al Kharga district, Egypt. *Neuropsychiatr Dis Treat* 2013, 9:1821-1826.

30. Sanchez JL, Buritica O, Pineda D, Uribe CS, Palacio LG: Prevalence of Parkinson's disease and parkinsonism in a Colombian population using the capture-recapture method. *Int J Neurosci* 2004, 114(2):175-182.

31. Khedr EM, Al Attar GS, Kandil MR, Kamel NF, Abo Elfetoh N, Ahmed MA: Epidemiological study and clinical profile of Parkinson's disease in the Assiut Governorate, Egypt: a community-based study. *Neuroepidemiology* 2012, 38(3):154-163.

32. Kruja J, Beghi E, Zerbi D, Dobi D, Kuqo A, Zekja I, Mijo S, Kapisyzi M, Messina P: High prevalence of major neurological disorders in two Albanian communities: results of a door-to-door survey. *Neuroepidemiology* 2012, 38(3):138-147.

33. Bower JH, Maraganore DM, McDonnell SK, Rocca WA: Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1990. *Neurology* 1999, 52(6):1214-1220.

34. Katzenschlager R, Head J, Schrag A, Ben-Shlomo Y, Evans A, Lees AJ: Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD. *Neurology* 2008, 71(7):474-480.

35. Wang YS, Shi YM, Wu ZY, He YX, Zhang BZ: Parkinson's disease in China. Coordinational Group of Neuroepidemiology, PLA. *Chin Med J (Engl)* 1991, 104(11):960-964.

36. de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meche FG, Hofman A: Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. *Neurology* 1995, 45(12):2143-2146.

37. von Campenhausen S, Bornschein B, Wick R, Botzel K, Sampaio C, Poewe W, Oertel W, Siebert U, Berger K, Dodel R: Prevalence and incidence of Parkinson's disease in Europe. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* 2005, 15(4):473-490.

38. Attia Romdhane N, Ben Hamida M, Mrabet A, Larnaout A, Samoud S, Ben Hamda A, Ben Hamda M, Oueslati S: Prevalence study of neurologic disorders in Kelibia (Tunisia). *Neuroepidemiology* 1993, 12(5):285-299.

39. Alrefai A, Habahbih M, Alkhawajah M, Darwish M, Batayha W, Khader Y, El-Salem K: Prevalence of Parkinson's disease in Northern Jordan. *Clinical neurology and neurosurgery* 2009, 111(10):812-815.

40. al Rajeh S, Bademosi O, Ismail H, Awada A, Dawodu A, al-Freihi H, Assuhaimi S, Borollosi M, al-Shammasi S: A community survey of neurological disorders in Saudi Arabia: the Thugbah study. *Neuroepidemiology* 1993, 12(3):164-178.

41. Muangpaisan W, Hori H, Brayne C: Systematic review of the prevalence and incidence of Parkinson's disease in Asia. *J Epidemiol* 2009, 19(6):281-293.

42. Fereshtehnejad SM, Shafieesabet M, Rahmani A, Delbari A, Lokk J: Medium-to-high prevalence of screening-detected parkinsonism in the urban area of Tehran, Iran: data from a community-based door-to-door study. *Neuropsychiatr Dis Treat* 2015, 11:321-332.

43. Chan DK, Cordato D, Karr M, Ong B, Lei H, Liu J, Hung WT: Prevalence of Parkinson's disease in Sydney. *Acta neurologica Scandinavica* 2005, 111(1):7-11.

44. Osuntokun BO, Adeuja AO, Schoenberg BS, Bademosi O, Nottidge VA, Olumide AO, Ige O, Yaria F, Bolis CL: Neurological disorders in Nigerian Africans: a community-based study. *Acta neurologica Scandinavica* 1987, 75(1):13-21.

45. Trenkwalder C, Schwarz J, Gebhard J, Ruland D, Trenkwalder P, Hense HW, Oertel WH: Starnberg trial on epidemiology of Parkinsonism and hypertension in the elderly. Prevalence of Parkinson's disease and related disorders assessed by a door-to-door survey of inhabitants older than 65 years. *Archives of neurology* 1995, 52(10):1017-1022.

46. Statistical Center of Iran. "Statistics, census of population and housing of the year 2011", visited at: http://www.amar.org.ir/Default.aspx?tabid=133 (accessed date: 26 October 2014)

47. Statistical Centre of Iran. 2006. [Population by Sex and Age Group: 1385 Census (2006)]. (http://amar.sci.org.ir/index_e.aspx) accessed 15 June 2011.

48. Noroozian M: The elderly population in iran: an ever growing concern in the health system. *Iranian journal of psychiatry and behavioral sciences* 2012, 6(2):1-6.

49. Danial Z, Motamedi MH, Mirhashemi S, Kazemi A, Mirhashemi AH: Ageing in iran. *Lancet* 2014, 384(9958):1927.

50. Lefton J, Malone A: Anthropometric Assessment. In Charney P, Malone A, eds. ADA Pocket Guide to Nutrition Assessment, 2nd edition. Chicago, IL: American Dietetic Association. 2009:160-161.

51. Crogan NL, Pasvogel A: The influence of protein-calorie malnutrition on quality of life in nursing homes. *J Gerontol A Biol Sci Med Sci* 2003, 58(2):159-164.

52. Neumann SA, Miller MD, Daniels L, Crotty M: Nutritional status and clinical outcomes of older patients in rehabilitation. *J Hum Nutr Diet* 2005, 18(2):129-136.

53. Lees AJ, Hardy J, Revesz T: Parkinson's disease. *Lancet* 2009, 373(9680):2055-2066.

54. Fahn S: Description of Parkinson's disease as a clinical syndrome. *Annals of the New York Academy of Sciences* 2003, 991:1-14.

55. Fereshtehnejad SM, Ghazi L, Sadeghi M, Khaefpanah D, Shahidi GA, Delbari A, Lokk J: Prevalence of malnutrition in patients with Parkinson's disease: a comparative study with healthy controls using Mini Nutritional Assessment (MNA) questionnaire. *Journal of Parkinson's disease* 2014, 4(3):473-481.

56. Walker RW, Dunn JR, Gray WK: Self-reported dysphagia and its correlates within a prevalent population of people with Parkinson's disease. *Dysphagia* 2011, 26(1):92-96.

57. Jost WH: Gastrointestinal motility problems in patients with Parkinson's disease. Effects of antiparkinsonian treatment and guidelines for management. *Drugs Aging* 1997, 10(4):249-258.

58. Barker LA, Gout BS, Crowe TC: Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system. *Int J Environ Res Public Health* 2011, 8(2):514-527.

59. Sheard JM, Ash S, Silburn PA, Kerr GK: Prevalence of malnutrition in Parkinson's disease: a systematic review. *Nutr Rev* 2011, 69(9):520-532.

60. Wang G, Wan Y, Cheng Q, Xiao Q, Wang Y, Zhang J, Ma JF, Wang XJ, Zhou HY, Chen SD: Malnutrition and associated factors in Chinese patients with Parkinson's disease: Results from a pilot investigation. *Parkinsonism Relat Disord* 2010, 16(2):119-123.

61. Barichella M, Villa MC, Massarotto A, Cordara SE, Marczewska A, Vairo A, Baldo C, Mauri A, Savardi C, Pezzoli G: Mini Nutritional Assessment in patients with Parkinson's disease: correlation between worsening of the malnutrition and increasing number of disease-years. *Nutr Neurosci* 2008, 11(3):128-134.

62. Amaral TF, Matos LC, Teixeira MA, Tavares MM, Alvares L, Antunes A: Undernutrition and associated factors among hospitalized patients. *Clin Nutr* 2010, 29(5):580-585.

63. Sheard JM, Ash S, Silburn PA, Kerr GK: Nutritional status in Parkinson's disease patients undergoing deep brain stimulation surgery: a pilot study. *J Nutr Health Aging* 2013, 17(2):148-151.

64. Sheard JM, Ash S, Mellick GD, Silburn PA, Kerr GK: Improved nutritional status is related to improved quality of life in Parkinson's disease. *BMC Neurol* 2014, 14:212.

65. Beyer PL, Palarino MY, Michalek D, Busenbark K, Koller WC: Weight change and body composition in patients with Parkinson's disease. *J Am Diet Assoc* 1995, 95(9):979-983.

66. Lorefalt B, Ganowiak W, Palhagen S, Toss G, Unosson M, Granerus AK: Factors of importance for weight loss in elderly patients with Parkinson's disease. *Acta neurologica Scandinavica* 2004, 110(3):180-187.

67. Uc EY, Struck LK, Rodnitzky RL, Zimmerman B, Dobson J, Evans WJ: Predictors of weight loss in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2006, 21(7):930-936.

68. Barichella M, Cereda E, Madio C, Iorio L, Pusani C, Cancello R, Caccialanza R, Pezzoli G, Cassani E: Nutritional risk and gastrointestinal dysautonomia symptoms in Parkinson's disease outpatients hospitalised on a scheduled basis. *Br J Nutr* 2013, 110(2):347-353.

69. Sheard JM, Ash S, Mellick GD, Silburn PA, Kerr GK: Markers of disease severity are associated with malnutrition in Parkinson's disease. *PLoS One* 2013, 8(3):e57986.

70. Markus HS, Tomkins AM, Stern GM: Increased prevalence of undernutrition in Parkinson's disease and its relationship to clinical disease parameters. *J Neural Transm Park Dis Dement Sect* 1993, 5(2):117-125.

71. Durrieu G, ME LL, Rascol O, Senard JM, Rascol A, Montastruc JL: Parkinson's disease and weight loss: a study with anthropometric and nutritional assessment. *Clin Auton Res* 1992, 2(3):153-157.

72. Sheard JM, Ash S, Mellick GD, Silburn PA, Kerr GK: Malnutrition in a sample of community-dwelling people with Parkinson's disease. *PLoS One* 2013, 8(1):e53290.

73. Fereshtehnejad SM, Ghazi L, Shafieesabet M, Shahidi GA, Delbari A, Lokk J: Motor, psychiatric and fatigue features associated with nutritional status and its effects on quality of life in Parkinson's disease patients. *PLoS One* 2014, 9(3):e91153.

74. Li H, Zhang M, Chen L, Zhang J, Pei Z, Hu A, Wang Q: Nonmotor symptoms are independently associated with impaired health-related quality of life in Chinese patients with Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2010, 25(16):2740-2746.

75. Wood-Dauphinee S: Assessing quality of life in clinical research: from where have we come and where are we going? *Journal of clinical epidemiology* 1999, 52(4):355-363.

76. Soh SE, Morris ME, McGinley JL: Determinants of health-related quality of life in Parkinson's disease: a systematic review. *Parkinsonism Relat Disord* 2011, 17(1):1-9.

77. Lohle M, Storch A, Reichmann H: Beyond tremor and rigidity: non-motor features of Parkinson's disease. *Journal of neural transmission* 2009, 116(11):1483-1492.

78. Wolters E: Non-motor extranigral signs and symptoms in Parkinson's disease. *Parkinsonism Relat Disord* 2009, 15 Suppl 3:S6-12.

79. Hinnell C, Hurt CS, Landau S, Brown RG, Samuel M: Nonmotor versus motor symptoms: how much do they matter to health status in Parkinson's disease? *Movement disorders : official journal of the Movement Disorder Society* 2012, 27(2):236-241.

80. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR: The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2011, 26(3):399-406.

81. Shearer J, Green C, Counsell CE, Zajicek JP: The impact of motor and non motor symptoms on health state values in newly diagnosed idiopathic Parkinson's disease. *Journal of neurology* 2012, 259(3):462-468.

82. Winter Y, von Campenhausen S, Gasser J, Seppi K, Reese JP, Pfeiffer KP, Botzel K, Oertel WH, Dodel R, Poewe W: Social and clinical determinants of quality of life in Parkinson's disease in Austria: a cohort study. *Journal of neurology* 2010, 257(4):638-645.

83. Wu Y, Guo XY, Wei QQ, Song W, Chen K, Cao B, Ou RW, Zhao B, Shang HF: Determinants of the quality of life in Parkinson's disease: results of a cohort study from Southwest China. *J Neurol Sci* 2014, 340(1-2):144-149.

84. Langston JW: The Parkinson's complex: parkinsonism is just the tip of the iceberg. *Ann Neurol* 2006, 59(4):591-596.

85. Wicks P, Stamford J, Grootenhuis MA, Haverman L, Ahmed S: Innovations in e-health. *Qual Life Res* 2014, 23(1):195-203.

86. Sieber BA, Landis S, Koroshetz W, Bateman R, Siderowf A, Galpern WR, Dunlop J, Finkbeiner S, Sutherland M, Wang H *et al*: Prioritized research recommendations from the National Institute of Neurological Disorders and Stroke Parkinson's Disease 2014 conference. *Ann Neurol* 2014, 76(4):469-472.

87. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975, 12(3):189-198.

88. Fereshtehnejad SM, Shafieesabet M, Rahmani A, Farhadi F, Hadizadeh H, Shahidi GA, Delbari A, Lokk J: A novel 6-item screening questionnaire for parkinsonism: validation

and comparison between different instruments. *Neuroepidemiology* 2014, 43(3-4):178-193.

89. Gasparoli E, Delibori D, Polesello G, Santelli L, Ermani M, Battistin L, Bracco F: Clinical predictors in Parkinson's disease. *Neurol Sci* 2002, 23 Suppl 2:S77-78.

90. Fahn S, Elton RL: UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent Developments in Parkinson's Disease. 2nd ed. Florham Park, NJ: Macmillan Healthcare Information. 1987:153-163.

91. Post B, Speelman JD, de Haan RJ, group CA-s: Clinical heterogeneity in newly diagnosed Parkinson's disease. *Journal of neurology* 2008, 255(5):716-722.

92. van Rooden SM, Colas F, Martinez-Martin P, Visser M, Verbaan D, Marinus J, Chaudhuri RK, Kok JN, van Hilten JJ: Clinical subtypes of Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2011, 26(1):51-58.

93. Espay AJ, Li JY, Johnston L, Chen R, Lang AE: Mirror movements in parkinsonism: evaluation of a new clinical sign. *Journal of neurology, neurosurgery, and psychiatry* 2005, 76(10):1355-1358.

94. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica* 1983, 67(6):361-370.

95. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD: The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of neurology* 1989, 46(10):1121-1123.

96. Marinus J, Visser M, Martinez-Martin P, van Hilten JJ, Stiggelbout AM: A short psychosocial questionnaire for patients with Parkinson's disease: the SCOPA-PS. *Journal of clinical epidemiology* 2003, 56(1):61-67.

97. Persson MD, Brismar KE, Katzarski KS, Nordenstrom J, Cederholm TE: Nutritional status using mini nutritional assessment and subjective global assessment predict mortality in geriatric patients. *Journal of the American Geriatrics Society* 2002, 50(12):1996-2002.

98. Peto V, Jenkinson C, Fitzpatrick R: PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. *Journal of neurology* 1998, 245 Suppl 1:S10-14.

99. Meneghini F, Rocca WA, Anderson DW, Grigoletto F, Morgante L, Reggio A, Savettieri G, Di Perri R: Validating screening instruments for neuroepidemiologic surveys: experience in Sicily. Sicilian Neuro-Epidemiologic Study (SNES) Group. *Journal of clinical epidemiology* 1992, 45(4):319-331.

100. Hunter CB, Aguilar LG, Nashatizadeh MM, Lay LF, Jankovic J: Evaluation of a Parkinson's disease screening questionnaire for use in a community-based setting. *Mov Disord* 2008, 23(Suppl 1):S361.

101. Rocca WA, Maraganore DM, McDonnell SK, Schaid DJ: Validation of a telephone questionnaire for Parkinson's disease. *Journal of clinical epidemiology* 1998, 51(6):517-523.

102. Bower JH, Howlett W, Maro VP, Wangai H, Sirima N, Reyburn H: A screening instrument to measure the prevalence of neurological disability in resource-poor settings. *Neuroepidemiology* 2009, 32(4):313-320.

103. World Health Organization: Research Protocol for Measuring the Prevalence of Neurological Disorders in Developing Countries. *Geneva, World Health Organization* 1981.

104. Tanner CM, Gilley DW, Goetz CG: A brief screening questionnaire for parkinsonism. *Ann Neurol* 1990, 28:267–268.

105. Duarte J, Claveria LE, de Pedro-Cuesta J, Sempere AP, Coria F, Calne DB: Screening Parkinson's disease: a validated questionnaire of high specificity and sensitivity. *Movement disorders : official journal of the Movement Disorder Society* 1995, 10(5):643-649.

106. Chan DK, Hung WT, Wong A, Hu E, Beran RG: Validating a screening questionnaire for parkinsonism in Australia. *Journal of neurology, neurosurgery, and psychiatry* 2000, 69(1):117-120.

107. Setthawatcharawanich S, Sathirapanya P, Phabphal K, Limapichat K: Short questionnaire for Parkinson's disease as a screening instrument. *Clinical neurology and neurosurgery* 2011, 113(10):885-888.

108. Sevillano MD, de Pedro-Cuesta J, Duarte J, Claveria LE: Field validation of a method for population screening of parkinsonism. *Movement disorders : official journal of the Movement Disorder Society* 2002, 17(2):258-264.

109. Azimian M, Shahvarughi Farahani A, Dadkhah A, Fallahpour M, Karimlu M: Fatigue severity scale: The psychometric properties of the Persian-version in patients with multiple sclerosis. . *Research Journal of Biological Sciences* 2009, 4:974–977.

110. Fereshtehnejad SM, Hadizadeh H, Farhadi F, Shahidi GA, Delbari A, Lokk J: Reliability and validity of the persian version of the fatigue severity scale in idiopathic Parkinson's disease patients. *Parkinson's disease* 2013, 2013:935429.

111. Montazeri A, Vahdaninia M, Ebrahimi M, Jarvandi S: The Hospital Anxiety and Depression Scale (HADS): translation and validation study of the Iranian version. *Health and quality of life outcomes* 2003, 1:14.

112. Fereshtehnejad SM, Farhadi F, Hadizadeh H, Shahidi GA, Delbari A, Lokk J: Cross-cultural validity, reliability, and psychometric properties of the persian version of the scales for outcomes in Parkinson's disease-psychosocial questionnaire. *Neurology research international* 2014, 2014:260684.

113. Ghazi L, Fereshtehnejad SM, Abbasi Fard S, Sadeghi M, Shahidi GA, Lokk J: Mini Nutritional Assessment (MNA) is Rather a Reliable and Valid Instrument to Assess Nutritional Status in Iranian Healthy Adults and Elderly with a Chronic Disease. *Ecology of food and nutrition* 2015:1-16.

114. Nojomi M, Mostafavian Z, Shahidi GA, Jenkinson C: Quality of life in patients with Parkinson's disease: Translation and psychometric evaluation of the Iranian version of PDQ-39. *Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences* 2010, 15(2):63-69.

115. Fereshtehnejad SM, Naderi N, Rahmani A, Shahidi GA, Delbari A, Lokk J: Psychometric study of the Persian short-form eight-item Parkinson's disease questionnaire (PDQ-8) to evaluate health related quality of life (HRQoL). *Health and quality of life outcomes* 2014, 12:78.

116. Ramaker C, Marinus J, Stiggelbout AM, Van Hilten BJ: Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2002, 17(5):867-876.

117. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease: The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. *Movement disorders : official journal of the Movement Disorder Society* 2003, 18(7):738-750.

118. Hoehn MM, Yahr MD: Parkinsonism: onset, progression and mortality. *Neurology* 1967, 17(5):427-442.

119. Schwab RS, England AC: Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson IML (Eds). Third Symposium on Parkinson's Disease. Edinburgh: E and S Livingstone. 1969:152-157.

120. Morgante L, Rocca WA, Di Rosa AE, De Domenico P, Grigoletto F, Meneghini F, Reggio A, Savettieri G, Castiglione MG, Patti F *et al*: Prevalence of Parkinson's disease and other types of parkinsonism: a door-to-door survey in three Sicilian municipalities. The Sicilian Neuro-Epidemiologic Study (SNES) Group. *Neurology* 1992, 42(10):1901-1907.

121. Fayers PM, Machin D: Quality of Life: Assessment, Analysis and Interpretation. Chichester, England: John Wiley and Sons. 2000.

122. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M: Age standardization of rates: a new WHO standard. *World Health Organization, GPE Discussion Paper Series: No31* 2001.

123. Bandalos DL, Boehm-Kaufman MR: Four common misconceptions in exploratory factor analysis. In: Lance, Charles E.; Vandenberg, Robert J. Statistical and Methodological Myths and Urban Legends: Doctrine, Verity and Fable in the Organizational and Social Sciences. Taylor & Francis.pp. 61–87. 2008.

124. Youden WJ: Index for rating diagnostic tests. *Cancer* 1950, 3(1):32-35.

125. Mitchell AJ: Sensitivity x PPV is a recognized test called the clinical utility index (CUI+). *European journal of epidemiology* 2011, 26(3):251-252; author reply 252.

126. Mitchell AJ: How Do We Know When a Screening Test is Clinically Useful? In: Screening for Depression in Clinical Practice: An Evidence-Based Guide. Mitchell AJ, Coyne JC (Eds) ISBN10: 0195380193 OUP 2009.

127. Rubin DB, Schenker N: Multiple imputation in health-care databases: an overview and some applications. *Stat Med* 1991, 10(4):585-598.

128. Hooper D, Coughlan J, Mullen M: Structural equation modelling: Guidelines for determining model fit. *Electronic Journal of Business Research Methods* 2008, 6(1):53-60.

129. Jenkinson C, Fitzpatrick R: Cross-cultural evaluation of the short form 8-item Parkinson's Disease Questionnaire (PDQ-8): results from America, Canada, Japan, Italy and Spain. *Parkinsonism Relat Disord* 2007, 13(1):22-28.

130. Katsarou Z, Bostantjopoulou S, Peto V, Kafantari A, Apostolidou E, Peitsidou E: Assessing quality of life in Parkinson's disease: can a short-form questionnaire be useful? *Movement disorders : official journal of the Movement Disorder Society* 2004, 19(3):308-312.

131. Franchignoni F, Giordano A, Ferriero G: Rasch analysis of the short form 8-item Parkinson's Disease Questionnaire (PDQ-8). *Qual Life Res* 2008, 17(4):541-548

132. Dal Bello-Haas V, Klassen L, Sheppard MS, Metcalfe A: Psychometric Properties of Activity, Self-Efficacy, and Quality-of-Life Measures in Individuals with Parkinson Disease. *Physiother Can* 2011, 63(1):47-57. doi: 10.3138/ptc.2009-3108. Epub 2011 Jan 3120.

133. Tan LC, Luo N, Nazri M, Li SC, Thumboo J: Validity and reliability of the PDQ-39 and the PDQ-8 in English-speaking Parkinson's disease patients in Singapore. *Parkinsonism Relat Disord* 2004, 10(8):493-499.

134. Martinez-Martin P, Benito-Leon J, Alonso F, Catalan MJ, Pondal M, Zamarbide I: Health-related quality of life evaluation by proxy in Parkinson's disease: approach using PDQ-8 and EuroQoL-5D. *Mov Disord* 2004, 19(3):312-318.

135. Tan LC, Lau PN, Au WL, Luo N: Validation of PDQ-8 as an independent instrument in English and Chinese. *J Neurol Sci* 2007, 255(1-2):77-80. Epub 2007 Mar 2002.

136. Huang TT, Hsu HY, Wang BH, Chen KH: Quality of life in Parkinson's disease patients: validation of the Short-Form Eight-item Parkinson's Disease Questionnaire (PDQ-8) in Taiwan. *Qual Life Res* 2011, 20(4):499-505

137. Mutch WJ, Smith WC, Scott RF: A screening and alerting questionnaire for parkinsonism. *Neuroepidemiology* 1991, 10(3):150-156.

138. Zhang ZX, Anderson DW, Huang JB, Li H, Hong X, Wei J, Yang EL, Maraganore DM: Prevalence of Parkinson's disease and related disorders in the elderly population of greater Beijing, China. *Movement disorders : official journal of the Movement Disorder Society* 2003, 18(7):764-772.

139. de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S, Manubens-Bertran JM, Alperovitch A, Rocca WA: Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry* 1997, 62(1):10-15.

140. Schrag A, Ben-Shlomo Y, Quinn NP: Cross sectional prevalence survey of idiopathic Parkinson's disease and Parkinsonism in London. *BMJ* 2000, 321(7252):21-22.

141. Bharucha NE, Bharucha EP, Bharucha AE, Bhise AV, Schoenberg BS: Prevalence of Parkinson's disease in the Parsi community of Bombay, India. *Archives of neurology* 1988, 45(12):1321-1323.

142. Alves G, Muller B, Herlofson K, HogenEsch I, Telstad W, Aarsland D, Tysnes OB, Larsen JP: Incidence of Parkinson's disease in Norway: the Norwegian ParkWest study. *Journal of neurology, neurosurgery, and psychiatry* 2009, 80(8):851-857.

143. Barichella M, Marczewska A, Vairo A, Canesi M, Pezzoli G: Is underweightness still a major problem in Parkinson's disease patients? *European journal of clinical nutrition* 2003, 57(4):543-547.

144. Petroni ML AG, Bicchiega V, Baudo S, Vinci C, Montesano A, et al: Body composition in advanced-stage Parkinson's disease. *Acta Diabetol* 2003, 40 Suppl 1:187-190.

145. Jaafar A, Porter B, Gray W, Turnbull E, Walker R: A study of the nutritional status of people with idiopathic Parkinson's disease: comparison of urban and rural community dwellers. *Mov Disord* 2010, 25 (Suppl 2):S424.

146. van der Marck MA, Dicke HC, Uc EY, Kentin ZH, Borm GF, Bloem BR, Overeem S, Munneke M: Body mass index in Parkinson's disease: a meta-analysis. *Parkinsonism Relat Disord* 2012, 18(3):263-267.

147. Serrano-Urrea R, Garcia-Meseguer MJ: Malnutrition in an Elderly Population without Cognitive Impairment Living in Nursing Homes in Spain: Study of Prevalence Using the Mini Nutritional Assessment Test. *Gerontology* 2013, 59(6):490-498.

148. Nozaki S, Saito T, Matsumura T, Miyai I, Kang J: [Relationship between weight loss and dysphagia in patients with Parkinson's disease]. *Rinsho shinkeigaku = Clinical neurology* 1999, 39(10):1010-1014.

149. Qin Z, Zhang L, Sun F, Fang X, Meng C, Tanner C, Chan P: Health related quality of life in early Parkinson's disease: impact of motor and non-motor symptoms, results from Chinese levodopa exposed cohort. *Parkinsonism Relat Disord* 2009, 15(10):767-771.

150. Rodriguez-Violante M, Cervantes-Arriaga A, Corona T, Martinez-Ramirez D, Morales-Briceno H, Martinez-Martin P: Clinical determinants of health-related quality of life in Mexican patients with Parkinson's disease. *Arch Med Res* 2013, 44(2):110-114.

151. Jones JD, Butterfield LC, Song W, Lafo J, Mangal P, Okun MS, Bowers D: Anxiety and Depression Are Better Correlates of Parkinson's Disease Quality of Life Than Apathy. *J Neuropsychiatry Clin Neurosci* 2014.

152. Kasten M, Kertelge L, Tadic V, Bruggemann N, Schmidt A, van der Vegt J, Siebner H, Buhmann C, Lencer R, Kumar KR *et al*: Depression and quality of life in monogenic compared to idiopathic, early-onset Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2012, 27(6):754-759.

153. Quelhas R, Costa M: Anxiety, depression, and quality of life in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 2009, 21(4):413-419.

154. Hong SK, Park KW, Cha JK, Kim SH, Chun DY, Yang CK: Quality of life in patients with Parkinson's disease. *J Korean Neurol Assoc* 2002, 2:227-233.

155. Behari M, Srivastava AK, Pandey RM: Quality of life in patients with Parkinson's disease. *Parkinsonism Relat Disord* 2005, 11(4):221-226.

156. Hristova DR, Hristov JI, Mateva NG, Papathanasiou JV: Quality of life in patients with Parkinson's disease. *Folia Med (Plovdiv)* 2009, 51(4):58-64.

157. Knipe MD, Wickremaratchi MM, Wyatt-Haines E, Morris HR, Ben-Shlomo Y: Quality of life in young- compared with late-onset Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2011, 26(11):2011-2018.

158. Zhao YJ, Tan LC, Lau PN, Au WL, Li SC, Luo N: Factors affecting health-related quality of life amongst Asian patients with Parkinson's disease. *Eur J Neurol* 2008, 15(7):737-742.

159. Visser M, van Rooden SM, Verbaan D, Marinus J, Stiggelbout AM, van Hilten JJ: A comprehensive model of health-related quality of life in Parkinson's disease. *Journal of neurology* 2008, 255(10):1580-1587.

160. Soh SE, McGinley JL, Watts JJ, Iansek R, Murphy AT, Menz HB, Huxham F, Morris ME: Determinants of health-related quality of life in people with Parkinson's disease: a path analysis. *Qual Life Res* 2013, 22(7):1543-1553.

161. Lee J, Choi M, Jung D, Sohn YH, Hong J: A Structural Model of Health-Related Quality of Life in Parkinson's Disease Patients. *West J Nurs Res* 2014.

162. Fereshtehnejad SM, Hadizadeh H, Farhadi F, Shahidi GA, Delbari A, Lokk J: Comparison of the Psychological Symptoms and Disease-Specific Quality of Life between Early- and Typical-Onset Parkinson's Disease Patients. *Parkinson's disease* 2014, 2014:819260.

163. Teasdale N, Hue O, Simoneau M, Tremblay A, Marceau P, Marceau S: Predictors of weight loss in Parkinson's disease: is weight loss the chicken or the egg? *Movement disorders : official journal of the Movement Disorder Society* 2007, 22(3):436-437.

164. Sheard JM, Ash S, Mellick GD, Silburn PA, Kerr GK: Nutrition screening and assessment in Parkinson's disease: A comparison of methods. *e-SPEN Journal* 2013, 8(5):e187–e192.

165. Mitchell AJ: Rapid screening for depression and emotional distress in routine cancer care: local implementation and meta-analysis Leicester: University of Leicester 2012.

166. Hancock G: Fortune cookies, measurement error, and experimental design. *J Mod Appl Stat Methods* 2003, 2(2):293–305.

167. GBD 2013 Mortality and Causes of Death Collaborators: Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015, 385(9963):117-171.

168. Few mild-to-moderate PD patients suffer from malnutrition, yet almost one third are at risk. [http://www.iospress.nl/ios_news/few-mild-to-moderate-pd-patients-suffer-from-malnutrition-yet-almost-one-third-are-at-risk/ (accessed 29 April 2015)]

Appendix 1. *List of all questions and the selected items (bold font with star-marked number) for the new screening instrument for parkinsonism used in study II*

NO.	Questions	Answer		
		No	Yes	Do not know
1	Have you ever had episodes of unconsciousness-that is, not understanding, not hearing, not seeing what was happening around you, and later not remembering what had happened during the loss of consciousness?	☐	☐	☐
2	Have you ever had uncontrolled movements of your legs or arms?	☐	☐	☐
3	Have there been serious changes in the way you speak?	☐	☐	☐
4	Has your face or part of your face ever been paralyzed for more than 24 hours?	☐	☐	☐
5	Has there ever been drooling from your mouth for more than 24 hours?	☐	☐	☐
6	Have you ever had weakness in your arms or legs for more than 24 hours?	☐	☐	☐
7	Have you ever had abnormal sensation as tingling, burning, or loss of feeling in your arms and legs for more than 24 hours or less time but more than once?	☐	☐	☐
8*	**Have you ever noticed stiffness in your legs?**	☐	☐	☐
9*	**Have you ever had tremors of your head, arms, or legs that lasted more than 1 day?**	☐	☐	☐
10	Is your handwriting smaller than it once was?	☐	☐	☐
11	Do you have trouble arising from a chair?	☐	☐	☐
12	Is your voice softer than it once was?	☐	☐	☐
13	Have you recently consulted a doctor about shoulder pain?	☐	☐	☐
14*	**Do you have trouble buttoning buttons or dressing?**	☐	☐	☐
15	Do you shuffle your feet and/or take smaller steps when you walk?	☐	☐	☐
16*	**Have you or others noted that you do not swing one arm when you walk?**	☐	☐	☐
17	Is your balance poor?	☐	☐	☐
18*	**Do your feet seem to get stuck to the floor when walking or turning?**	☐	☐	☐
19	Have you or others noted that you stoop or have abnormal posture?	☐	☐	☐
20	Has your ability to smell changed?	☐	☐	☐
21	Do you have dreams that make you act by screaming or fighting in your sleep?	☐	☐	☐
22	Do you have trouble concentrating or remembering?	☐	☐	☐
23*	**Have you become slower in your usual daily activities?**	☐	☐	☐
24	Do people tell you that your face seems less expressive than it once did?	☐	☐	☐
25	Have you been unable to walk properly?	☐	☐	☐