

University of Groningen

Apathy, fatigue and quality of life in patients with Parkinson's disease

Skorvanek, Matej

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2014

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Skorvanek, M. (2014). *Apathy, fatigue and quality of life in patients with Parkinson's disease*. [Thesis fully internal (DIV), University of Groningen]. [S.n.].

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Discussion

Research in the last decades has led to a shift of our understanding of Parkinson's disease (PD): from a pure 'motor' disorder caused by dopaminergic pathology to a progressive multisystem or multi-organ disease. Special interest has been recently paid especially to the non-motor symptoms (NMS) of PD, which are very frequent and are common across all stages of the disease (1). It has become increasingly clear that a number of non-motor features can precede the motor symptoms of PD, sometimes by many years (2). NMS in PD may have a major impact on the daily activities of patients, and the overall burden of NMS seems to be more important in determining the QoL of PD patients than the motor symptoms themselves (3,4). Due to a large number of NMS in PD several comprehensive tools have been developed for their assessment, including the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Some of the most frequent and bothersome NMS in PD include fatigue, apathy and depression, which have a high coincidence and can be confused with each other.

The aim of this thesis was to validate the Slovak translation of the MDS-UPDRS as a comprehensive tool for assessing the burden of NMS in PD and to explore the relationships between different NMS examined by the MDS-UPDRS and QoL. Furthermore, the aim of the thesis was to better describe the associations between fatigue, apathy and depression and to disentangle the implications that apathy and depression may have on the development of fatigue in PD. In this final chapter the main findings will be summarized (8.1) and discussed (8.2); furthermore, the strengths and limitations of the thesis will be discussed (8.3), and finally, the chapter will be completed with practical implications and recommendations for future research (8.4).

8.1 Main findings

8.1.1 Research question 1

Can the factor structure of the original English version of the MDS-UPDRS be proven also in the Slovak translation of the MDS-UPDRS in a confirmatory factor analysis?

The Movement Disorder Society (MDS) sponsored a revision of the original UPDRS – the MDS-UPDRS, which was published in 2008 (5). The

main aim of this revision was to address the shortcomings of the original scale, to improve the scale properties and to cover a larger number of PD manifestations, particularly including some non-motor symptoms (NMS) which were not part of the original scale. Recently, the MDS launched an official program for translation and validation of the MDS-UPDRS in other languages, including the Slovak language. We found that the overall factor structure of the Slovak version was consistent with that of the English version based on confirmatory factor analyses (CFA) for all four parts of the MDS-UPDRS (all CFI > 0.91). The Slovak scale was found to share a common factor structure with the English scale. Therefore, the Slovak version was designated as the official Slovak version of the MDS-UPDRS. In the exploratory factor analysis, where variability from sample to sample is expected, we identified isolated item differences of the factor structure between the Slovak and English version of MDS-UPDRS, especially in Part II (motor experiences of daily living). Half of the items loaded differently and several items had cross loading on multiple factors in the Slovak scale.

8.1.2 Research question 2

How does the MDS-UPDRS correlate to QoL and which MDS-UPDRS non-motor items are the most relevant regarding worse QoL?

Our results show that the MDS-UPDRS Part II (motor experiences of daily living -mEDL), Part I (non-motor experiences of daily living - nmEDL) and Part IV (motor complications - MCompl) were significantly related to worse QoL, whereas Part III (motor examination - MEx) was not. Furthermore, we explored the relationship between individual MDS-UPDRS non-motor items and QoL. Individual MDS-UPDRS non-motor items related to the PDQ39 summary index were Pain and other sensations and Fatigue and Features of dopamine dysregulation syndrome (DDS). Other MDS-UPDRS non-motor items – e.g. Depressed mood, Anxious mood, Apathy, Cognitive impairment, Hallucinations and psychosis, Sleep problems, Daytime sleepiness and Urinary problems – were related to some PDQ39 domains, while the MDS-UPDRS items Constipation problems and Light-headedness on standing were not related to any PDQ39 domain. The motor symptoms as evaluated by the MDS-UPDRS part III (MEx) as well as the disease duration were not related to worse QoL in a multiple regression analysis model with the four MDS-UPDRS components, but they were significantly associated in a model with individual MDS-UPDRS non-motor items, confirming the importance of the concept of overall NMS burden in PD.

8.1.3 Research question 3

Is fatigue in the absence of depression and excessive daytime sleepiness (primary fatigue) different from fatigue in the presence of depression or excessive daytime sleepiness (secondary fatigue) and can they be distinguished?

Both depression and excessive daytime sleepiness (EDS) have been linked to fatigue in previous studies, and in fact they present confounding factors for the evaluation of fatigue, as these symptoms may overlap considerably. Our results show that the clinical determinants of these two types of fatigue differ significantly. In the secondary fatigue group older age was strongly associated with higher reduced motivation and mental fatigue scores. Male gender was related to higher reduced activity and mental fatigue. UPDRS-III was significantly associated with more fatigue in all domains except mental fatigue, and anxiety was associated with reduced motivation. Depression and sleep problems were not associated with any Multidimensional Fatigue Inventory (MFI) domain in this group. In the primary fatigue group the only variable significantly associated with MFI reduced activity and mental fatigue domains was BDI-II, although within the normality range. A similar relation was also found between HADS-D and fatigue within the normality range when the sample was divided according to HADS-D (≤ 10 pts) instead of BDI. Motor symptoms in PD (UPDRS part III) were not associated with any of the MFI domains in the primary fatigue group. Also, there were no determinants related to general fatigue, physical fatigue and reduced motivation in this group. Our results show that primary and secondary fatigue can be distinguished and should be considered as separate constructs in future studies.

8.1.4 Research question 4

What are the clinical determinants of apathy in the elderly non-demented PD population, can apathy in this population be distinguished from depression and is apathy relevant regarding QoL in elderly PD patients?

Our results show that apathy and depression can be dissociated in elderly non-demented PD patients, although the coincidence of apathy with depression in our study was higher than was reported in previous studies from the general PD population and using the same methodology for the assessment of both depression (BDI-II) and apathy (AS). The most important factors related to apathy in our study were higher depression scores and lower L-dopa equivalent daily dosage (LEDD). Previous studies have reported a correlation between apathy and worse QoL in the PD population. In our study apathy in a model without depression and without anxiety was significantly related to worse QoL; however, when depression and anxiety were added, this relationship was not significant for apathy specifically in the elderly non-demented PD population.

8.1.5 Research question 5

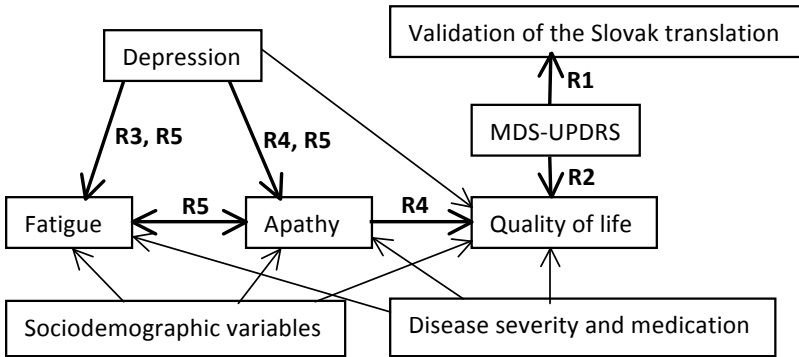
What is the relationship between fatigue, apathy and depression in PD, can they be distinguished and what implications may apathy and depression have on the development of fatigue in Parkinson's disease?

As shown in our study, the prevalence and severity of fatigue and apathy were significantly higher in depressed PD patients. However, our results show that depression, fatigue and apathy can be clearly distinguished in PD, as patients with pure depression, pure apathy and pure fatigue were found in all domains in the study. In multiple regression analyses, apathy was associated with the MFI's reduced motivation domain in both depressed and non-depressed patients. However, apathy was associated with mental fatigue aspects only in non-depressed patients, and it was not related to the physical aspects of fatigue in any of the studied groups. Moreover, apathy was the only clinical determinant of the mental aspects of fatigue in the non-depressed patients in our study, while these were rather related to older age and lower education level in the depressed patients. Apathy was not related to the physical aspects of fatigue in either depressed or non-depressed patients.

8.2 Discussion of the main findings

QoL is an important concept in the management of chronic diseases, including PD. As shown in our study, the overall burden of NMS in PD, rather than individual NMS, seems to be more important than the motor status in this regard. This finding is in accordance with some previous reports (3,6), including the study of Martinez-Martin et al. (4) which assessed the relationship of MDS-UPDRS parts I-IV with QoL measures. Their results showed that MDS-UPDRS Part I (nmEDL) and Part II (mEDL) were significantly related to worse QoL, whereas Part III (MEx) and Part IV (MCompl) were not. Our results are partly in line with these findings, as the MDS-UPDRS components significantly related to QoL were part I (nmEDL) and part II (mEDL), but in contrast to the above-mentioned study also part IV (MCompl), whereas part III (MEx) was not. The importance of motor fluctuations found in our study could be potentially explained by enrollment of a bigger proportion of fluctuating patients compared with the sample of Martinez-Martin et al. (4), since part of our sample was also enrolled during the UDysRS validation study, and our findings are in line with some other previous reports showing the importance of motor fluctuations and dyskinesias regarding QoL (7,8).

Figure 8.1 Model of the relationships examined in the thesis based on the previously formulated research questions



Relationship of individual NMS (Pain, Features of DDS, Depression) and QoL

The MDS-UPDRS was designed by an MDS working group of experts in the field to cover the most important non-motor aspects of PD and to be used as a comprehensive tool for assessment of the overall NMS burden in PD (5). The MDS-UPDRS items are designed not only to detect the presence of the NMS but also to assess the severity and impact of the particular NMS on a patient's functioning, therefore making it a viable tool for correlations with QoL measures. In our study, we have identified Pain and Fatigue and Features of DDS as the most important non-motor items of the MDS-UPDRS regarding QoL. However, other NMS items, such as Depressed mood, Anxious mood, Apathy, Cognitive impairment, Hallucinations and psychosis, Sleep problems, Daytime sleepiness and Urinary problems, were also related to some QoL aspects.

Pain was the strongest predictor of worse QoL in our study, which is in line with previous studies where pain has been repeatedly related to worse QoL in PD patients (3,9). Moreover, pain is one of the most common NMS in PD and can be present in over 80% of the patients (10). Pain in PD can be categorized into a number of different subtypes, including musculoskeletal, dystonic, radicular neuropathies and central pain, which highlights the multifactorial etiology of pain in PD, which can be related directly to the hypodopaminergic syndrome and indirectly to the motor PD symptoms or to other central mechanisms (10). Pain in PD was also previously related to depression, which even highlights the importance of pain in PD symptomatology regarding QoL (11).

Features of dopamine dysregulation syndrome (DDS) are another NMS with a significant relationship to worse QoL in our study. The term DDS itself more commonly refers to the compulsive use of

dopaminergic medications well beyond the dose needed to optimally control motor disability; however, this MDS-UPDRS item was designed to address a broader spectrum of impulsive and compulsive behaviours, including impulse control disorders (ICDs - such as excessive gambling or hypersexuality) and punding (5). The ICDs are usually linked to the dopaminergic medication, especially dopamine agonists. Although the prevalence of ICDs in PD is estimated to be only around 14%, the presence of these symptoms may have a severe and devastating impact on the personal and family life of the affected individuals (12). Interestingly, the impact of DDS on the overall QoL found in our study was even more important than that of the NMS traditionally linked to worse QoL, such as mood and sleep disorders, thus highlighting the importance of this issue, which has only been addressed in a few previous studies (13,14).

Depression, which has been a consistent and significant determinant of worse QoL in most previous studies (1,3,9), including our sample of elderly PD patients (15), was not related to the PD39 summary index score when assessed by the MDS-UPDRS item Depressed mood, although it was related to some PDQ39 subdomains. This may be related to the enrollment of a higher number of NMS which were not part of many QoL studies, such as fatigue, pain, DDS and others, all of which have also been previously associated with depression in PD (10,14,16,17), therefore partially confounding this relationship.

Fatigue – relationship to QoL and clinical determinants

Fatigue was one of the most important determinants of a worse overall QoL in our study, which is in line with most previous studies (1,3,18). Fatigue is one of the most common NMS associated with Parkinson's disease (PD), with a prevalence of up to 80% among PD patients (19). It is present in all stages of PD and in some cases even precedes the onset of the motor symptoms by years (20). In one of the first studies on fatigue in PD, 15-33% of patients rated it as their most disabling symptom, and more than half rated fatigue among their three worst symptoms (21). In a recent study among veterans with PD, patients rated fatigue and pain as having the greatest impact on their daily activities, which is in line with our findings (22). Also, in a study which examined the treatment expectations of PD patients, fatigue was found to be the third most relevant problem (23). Despite its high prevalence and importance, fatigue in PD remains an under-recognized problem in routine clinical practice (24). This is also highlighted by the lack of a clear definition of fatigue in PD, which can be generally divided into 'peripheral fatigue', which refers to an objectively measurable process in which a muscle loses strength after repeated contractions, and 'central fatigue', which refers to a feeling-state, perception or experience that is not yet objectively measurable. In addition, central fatigue can be further divided into physical and mental

fatigue domains and is more difficult to objectively assess compared with peripheral fatigue (25).

The factors most commonly associated with fatigue in previous studies are depression (26,27) and excessive daytime sleepiness (EDS) (28,29), which may in many cases be confounded with fatigue. Moreover, fatigue presents one of the DSM-IV criteria for the diagnosis of depression, thus making their delineation problematic. Based on this overlap we have formulated a concept of 'primary' fatigue, which is defined as fatigue in the absence of depression and excessive daytime sleepiness, and 'secondary' fatigue, defined as fatigue in the presence of either depression or excessive daytime sleepiness, as these probably present different concepts in PD and are based on different underlying mechanisms (16). As found in our study, fatigue was more prevalent and more severe in the 'secondary' fatigue group; however, it was associated with different clinical and sociodemographic determinants. While secondary fatigue in different domains was related to disease severity, anxiety, older age and male gender, primary fatigue was not related to any sociodemographic variables or disease severity, and the only determinant of the mental fatigue domains were higher depression scores, although within the normality range (16). The association between fatigue and motor symptoms as well as with other sociodemographic variables has been inconsistent in previous studies (26,27), probably as a result of the inclusion of different patient samples as seen in our study, making the differentiation between primary and secondary fatigue an important concept for future PD studies.

Apathy – relationship to QoL and clinical determinants

A similar relationship with depression, as that seen in fatigue, has been reported in PD-related apathy, which also represents one of the DSM-IV criteria for diagnosing depression. Some previous studies have addressed the issue of whether apathy and depression represent a single entity or discrete construct. In fact, up to 33% of PD patients may experience apathy without depression (30), and multiple studies have suggested that apathy and depression in PD can be clearly dissociated (31-33). The etiology of apathy in PD is clearly multifactorial, and it partly correlates with cognitive dysfunction, particularly executive dysfunctions as shown in a study by Dujardin et al. (34), where non-demented apathetic patients had a significantly higher rate of conversion to dementia later in the disease course than non-apatetic patients. While cognitive deterioration is more common especially in the elderly population, no previous studies have assessed apathy specifically in the non-demented elderly PD population, which is at a relatively higher risk for the development of cognitive dysfunction as such. This highlights the importance of the presence of apathy as a risk factor for such deterioration in this group of patients. This

was addressed in our study (15), which found that apathy can be clearly distinguished from depression in elderly PD patients, too, although the overlap between these NMS seems to be higher than in the previous studies dissociating both of these symptoms using the same methodology (31-33). The most important determinants of apathy in this group of patients were depression and lower L-dopa equivalent daily dosage. These findings are in line with previous studies in non-demented PD patients, where apathy was etiologically linked either to depression or to hypodopaminergic syndrome. The dopamine depletion theory is supported by the fact that apathy is a common finding in early untreated PD (35), and some previous studies suggest that dopamine agonists, e.g. priribedil, as well as levodopa may improve apathy (36,37). Apathy as a consequence of a dopamine withdrawal syndrome was suggested in some previous studies (38,39), including a study of 63 patients with PD after subthalamic deep brain stimulation, where 34 patients became apathetic after the dopaminergic medication was reduced by 82% within 2 weeks after surgery (39). In this study a subgroup of patients underwent a ¹¹C-raclopride positron emission tomography (PET) study, and patients with apathy showed increased binding bilaterally in the orbitofrontal cortex, the posterior cingulate cortex, the left dorsolateral prefrontal cortex, the bilateral striatum, the left thalamus and the right amygdala, suggesting that an increase of D2/D3 receptors or a reduction of synaptic dopamine levels might be related to subthalamic nucleus deep brain stimulation (STN-DBS) induced apathy. These findings suggest that in selected patients with PD displaying no cognitive deterioration, postoperative apathy can be seen as a model of a pure mesolimbic hypodopaminergic syndrome, which is unmasked by postoperative drug withdrawal (39). The pathophysiology of apathy is, however, clearly multifactorial, as not all patients with Parkinson's disease or dopaminergic depletion develop apathy.

In a study of recently diagnosed PD patients, apathetic patients were 2.5-times more likely to have lower QoL compared with non-apathetic PD patients after adjusting for sociodemographic factors and disease variables (40). Apathy has also been previously associated with a worse 39-item Parkinson's Disease Quality of Life Questionnaire (PDQ39) total score and the PDQ39 cognition and stigma subdomains (41). Our results, specifically in elderly non-demented PD patients, did not show a significant relationship of apathy to worse QoL when controlled for depression and anxiety, and the MDS-UPDRS item Apathy in our general PD population was also not related to the PDQ39 summary index score, although it was related to the PDQ39 domain Stigma. Nevertheless, apathy remains an important feature of PD, as multiple previous studies have shown that it belongs to a more severe phenotype of PD, that it may be a predictor of cognitive decline and that it may significantly increase the caregiver burden (34,35,40-42).

Relationship between fatigue and apathy in PD

Despite the high coincidence of fatigue and apathy in PD, studies correlating these two non-motor symptoms are surprisingly very scarce. In a study by Funkiewicz et al. (43) PD patients after DBS often confused apathy with fatigue: they reported feeling tired and having difficulties in starting any activities. The only study which has thus far directly correlated fatigue with different apathy domains showed that fatigue in their PD sample was significantly associated with the Lille Apathy Rating Scale total score, as well as with the intellectual curiosity and action initiation sub-scores (44). However, no study to date has evaluated the relationship of apathy to different fatigue domains. Moreover, the relationship between apathy and fatigue in PD is most likely influenced by the presence or absence of depression, as both of these symptoms are part of the DSM-IV criteria for diagnosing depression (41,45). This issue has been addressed in our study, which confirmed that fatigue, apathy and depression can be also distinguished, as patients with pure fatigue, pure apathy and pure depression can be found in PD. On the other hand, apathy was found to be the only clinical determinant of the mental fatigue domains in non-depressed patients. This correlation between fatigue and apathy in PD is not clear. While apathy in non-depressed patients has been mostly linked to a dopaminergic denervation in the mesolimbic structures, as mentioned above, fatigue was previously linked rather to serotonergic deficits (46). This PET study (46) performed in PD patients with primary fatigue found reduced serotonin transporter binding in the caudate, putamen, ventral striatum, thalamus, cingulate and amygdala, and concluded that fatigue in PD is associated with reduced serotonergic function of the basal ganglia and limbic structures. This study, however, was conducted only with a small number of participants, and the results were not specifically correlated with physical or mental aspects of fatigue. Therefore, it remains unclear whether serotonergic dysfunction in these regions is associated with PD-related fatigue as such, or with some of its specific aspects. On the other hand, the mentioned study also found a reduced 18F-dopa uptake in the caudate and insula, which could point to a potential role of the dopaminergic system in at least some aspects of primary fatigue in PD (46). In fact, the role of dopaminergic dysfunction in PD-related primary fatigue might also be supported by some previous reports showing improvement of fatigue after the initiation of dopaminergic therapy in some of the studied PD patients (20,47).

Apathy in PD may be present after direct lesions to both the prefrontal cortex (PFC) and basal ganglia, and it clearly presents a consequence of the disruption of the PFC-basal ganglia axis (48). Recently, de la Fuente-Fernandez (49) proposed a fronto-striatal cognitive dysfunction staging divided into three stages, which reflects a sequential process of dopamine depletion occurring in different regions of the striatum (stages I and II)

and the frontal cortex (stage III). In this staging system, among other symptoms, mental fatigue is attributed to stage I and apathy to stage IIb, and although the concept of mental fatigue in this staging system is not fully explained in this study, it presents an interesting framework for further hypothesis-testing and another potential link between PD-related apathy and fatigue. The potential role of the dopaminergic system as well as of the disruption of the PFC-basal ganglia axis in the pathophysiology of both fatigue and apathy in at least some PD patients might also be supported by results of some previous studies with methylphenidate in PD (50-52). Methylphenidate is a CNS stimulant that blocks the presynaptic dopamine transporter (DaT) and the noradrenaline transporter in the striatum, and in the PFC in particular (51). Based on these findings we suggest that apathy and mental fatigue in non-demented PD patients may be linked via three axis – depression (31-33,41), dopaminergic depletion in the mesolimbic structures (39,53-55) and disruption of the PFC-basal ganglia axis (48,49).

8.3 Strengths and limitations

For Chapters 3 and 4, the multicenter sample including patients in all stages of the disease from the initial to the very late stages as well as the use of validated and reliable measures represent the strengths of this study. For Chapters 5-7, all patients were examined by a single movement disorder neurologist, which ensured exclusion of non-PD subjects and a uniform evaluation of their motor status, preventing an inter-rater examination bias; in addition, all scales used have been previously validated and recommended for use in PD (56). The study also has some limitations. The dissociation of fatigue, apathy and depression was not done by a full psychiatric interview, but rather by self-report questionnaires; however, all instruments used have been validated and repeatedly utilized for the purpose of distinguishing fatigue, apathy and depression in patients with PD. Moreover, they have been recommended for use in PD patients by the Movement Disorder Society (56). The sample consisted of more motivated patients who agreed to participate in the study and who were able to attend the examination. The cross-sectional design of the study does not allow us to further explore the causal pathways between the studied variables. Also, the absence of demented patients in our sample does not allow us to generalize the results to the whole PD population.

8.4 Implications for future research and clinical practice

Compared with the original UPDRS, the MDS-UPDRS covers a larger number of motor, as well as non-motor PD manifestations; it better discriminates the slight and mild manifestations of the disease and is therefore more suitable for the initial stages of PD and potential trials

on disease modifying treatments; it better describes motor fluctuation; compared with the original UPDRS all individual items have a uniform scoring system; and thanks to accessible teaching instruments it enables a potentially higher inter-rater reliability (5). Moreover, the validity and reliability of this scale has been confirmed in multiple other independent studies and in different languages (57-59); therefore, we suggest that using the MDS-UPDRS in routine clinical practice as well as research settings is preferable in comparison with the original UPDRS.

The overall burden of NMS seems to be more important in relation to QoL than the motor symptomatology in treated PD patients (4); therefore, active screening and management of NMS is crucial. The MDS-UPDRS is one of the potential comprehensive tools to be used for the assessment of NMS. Other such tools for the assessment of NMS include the NMSQuest and the NMSS mentioned in the introduction of this thesis. The NMS which seem to be particularly important in determining QoL in PD are Pain, Fatigue and Features of DDS; however, other symptoms, such as mood and sleep disorders, cognitive problems, hallucinations, apathy and urinary problems, are also important for certain aspects of QoL (3,9). Moreover NMS such as apathy may not only impact the QoL of patients but may also significantly increase the caregiver burden (13) and may impact coping strategies of patients resulting in further worsening of QoL (60). Despite the different possibilities regarding treatments for motor symptoms of PD, management options for the NMS are usually less effective (61). While some of the NMS may respond to optimization of dopaminergic medication, others are caused rather by dysfunctions in other neurotransmitter systems and/or other organ dysfunctions, and therefore future development of specific therapies for these NMS is one of the major issues in PD.

Some of the most common and disabling NMS in PD include fatigue, apathy and depression. As shown in this thesis, both fatigue and apathy are partly related to depression; however, all of these symptoms can be clearly distinguished and represent different entities. We therefore suggest that distinguishing primary and secondary fatigue as well as pure apathy vs. depression-related apathy is very important in future studies in order to avoid the bias caused by the inclusion of different and unrelated patient samples. Moreover, recognizing that both fatigue and apathy can be present even without depression is important in order to prevent an incorrect diagnosis and unnecessary treatment as a depressive disorder. The etiology of both fatigue and apathy is clearly multifactorial, and besides their relation to depression, both primary fatigue and apathy in PD seem to also be partly related to dopaminergic pathology. However, especially in the case of primary fatigue, it remains unclear whether the serotonergic deficits contribute more to pure fatigue without apathy, while the dopaminergic pathology would rather contribute to

primary mental fatigue in coincidence with apathy as discussed above. This issue is certainly in need of further investigation. Further clinical, neurophysiological and imaging studies should be performed especially in primary fatigue and primary apathy in order to better understand their relationship and underlying pathophysiological mechanisms. Also, a longitudinal follow-up of patients is crucial in order to better understand the causal pathways between these NMS. Structural equation modeling could be also performed in this regard (17). Moreover, apathy is also clearly related to cognitive dysfunction, and further longitudinal studies in elderly apathetic patients with PD should be conducted in order to better understand the time frame and frequency of the potential conversion of apathy to dementia.

Clinical management of both fatigue and apathy in PD may be challenging. However, optimization of dopaminergic medications may lead to reduction of fatigue and apathy in some patients, as previous studies have shown their reduction after initiation or adjustment of the dopaminergic treatment, including both levodopa as well as dopamine agonists rotigotine and priribedil (20,37,47). Moreover, optimal management of depression, if present, may also lead to partial improvement of these symptoms. Further clinical trials with methylphenidate should be performed to better understand its position in the treatment of fatigue and apathy. Other specific treatments should be developed in the future to better address the management of both PD-related fatigue and apathy.

References:

1. Valkovic P, Harsany J, Hanakova M, et al. Nonmotor symptoms in early- and advanced-stage Parkinson's disease patients on dopaminergic therapy: how do they correlate with quality of life? *ISRN Neurology* 2014; doi: 10.1155/2014/587302
2. Lim SY, Lang AE. The non-motor symptoms of PD – an overview. *Movement Disord* 2010; 25:S123-S130.
3. Martinez-Martin P, Rodriguez-Blazquez C, Kurtis M, et al. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Movement Disord* 2011;26:399-406.
4. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, et al. Relationship between the MDS-UPDRS domains and the health-related quality of life of Parkinson's disease patients. *Eur J Neurol* 2014;21:519-524.
5. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement Disord* 2008;15:2129-2170.
6. Martinez-Martin P, Schapira AHV, Stocchi F, et al. Prevalence of

- nonmotor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. *Movement Disord* 2007; 22:1623-1629
7. Chaptuis S, OuchChane L, Metz O, et al. Impact of the motor complications of Parkinson's disease on the Quality of Life. *Movement Disord* 2005;20:224-230.
 8. Manson A, Stirpe P, Schrag A. Levodopa-induced-dyskinesias clinical features, incidence, risk factors, management and impact on quality of life. *J Parkinson Dis* 2012;2:189-198.
 9. Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? *Movement Disord* 2010;25:2493-2500.
 10. Ha AD, Jankovic J. Pain in Parkinson's disease. *Movement Disord* 2012;27:485-491.
 11. Santos-Garcia D, Abella-Corral J, Aneiros-Diaz A, et al. Pain in Parkinson's disease: prevalence, characteristics, associated factors, and relation with other non-motor symptoms, quality of life, autonomy and caregiver burden. *Rev Neurologia* 2011;52:385-393.
 12. Evans AH, Strafella AP, Weintraub D, et al. Impulsive and compulsive behaviors in Parkinson's disease. *Movement Disord* 2009;24:1561-1570.
 13. Leroi I, Ahearn DJ, Andrews M, et al. Behavioral disorders, disability and quality of life in Parkinson's disease. *Age Ageing* 2011;40:614-621.
 14. Phu AL, Xu Z, Brakoulias V, et al. Effect of impulse control disorders on disability and quality of life in Parkinson's disease patients. *J Clin Neurosci* 2014;21:63-66.
 15. Skorvanek M, Rosenberger J, Gdovinova Z, et al. Apathy in elderly non-demented patients with Parkinson's disease: Clinical determinants and relationship to quality of life. *J Geriatr Psych Neurol* 2013;26:237-243.
 16. Skorvanek M, Nagyova I, Rosenberger J, et al. Clinical determinants of primary and secondary fatigue in patients with Parkinson's disease. *J Neurol* 2013;260:1554-61.
 17. Van Dijk JP, Havlikova E, Rosenberger J, et al. Influence of disease severity on fatigue in patients with Parkinson's disease is mainly mediated by symptoms of depression. *Eur Neurol* 2013;70:201-209.
 18. Havlikova E, Rosenberger J, Nagyova I, et al. Impact of fatigue on quality of life in patients with Parkinson's disease. *Eur J Neurol* 2008;15:475-480.
 19. Skorvanek M, Rosenberger J, Gdovinova Z, et al. The associations between fatigue, apathy and depression in Parkinson's disease. *Acta Neurol Scand* 2014; accepted June 26 2014.
 20. Schifitto G, Friedman JH, Oakes D, et al. Fatigue in levodopa-naive subjects with Parkinson disease. *Neurology* 2008;71:481-485.

21. Friedman JH, Friedman H. Fatigue in Parkinson's disease. *Neurology* 1993;43:2016-2018.
22. Trail M, Peterson NJ, Nelson N, et al. An exploratory study of activity in veterans with Parkinson's disease. *J Neurol* 2012;259:1686-1693.
23. Nisenzon AN, Robinson ME, Bowers D, et al. Measurement of patient-centered outcomes in Parkinson's disease: What do patients really want from their treatment? *Parkinsonism Relat D* 2011;2:89-94.
24. Schulman LM, Taback R, Rabinstein AA, et al. Nonrecognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat D* 2002;8:193-197.
25. Friedman JH, Abrantes A, Sweet LH. Fatigue in Parkinson's disease. *Expert Opin Pharmacol* 2011;13:1999-2007.
26. Karlsen K, Larsen JP, Tandberg E, Jorgensen K. Fatigue in patients with Parkinson's disease. *Movement Disord* 1999;14:237-241.
27. Havlikova E, Rosenberger J, Nagyova I, et al. Clinical and psychosocial factors associated with fatigue in patients with Parkinson's disease. *Parkinsonism Relat D* 2008;14:187-192.
28. Alves G, Wentzel-Larsen T, Larsen JP. Is fatigue an independent and persistent symptom in patients with Parkinson's disease? *Neurology* 2004;63:1908-1911.
29. Valko PO, Waldvogel D, Weller M, et al. Fatigue and excessive daytime sleepiness in idiopathic Parkinson's disease differently correlate with motor symptoms, depression and dopaminergic treatment. *Eur J Neurol* 2010;17:1428-1436.
30. Cubo E, Benito-Leon J, Coronell C, et al. Clinical correlates of apathy in patients recently diagnosed with Parkinson's disease: the ANIMO Study. *Neuroepidemiology* 2012; 38:48-55.
31. Kirsch-Darrow L, Fernandez HF, Marsiske M, et al. Dissociating apathy and depression in Parkinson disease. *Neurology* 2006;1:33-38.
32. Kirsch-Darrow L, Marsiske M, Okun MS, et al. Apathy and depression: separate factors in Parkinson's disease. *J Int Neuropsychol Soc* 2011;17:1058-1066.
33. Ziropadja Lj, Stefanova E, Petrovic M, et al. Apathy and depression in Parkinson's disease: the Belgrade PD study report. *Parkinsonism Relat D* 2012;18:339-342.
34. Dujardin K, Sockeel P, Delliaux M, et al. Apathy may herald cognitive decline and dementia in Parkinson's disease. *Movement Disord* 2009; 16:2391-2397
35. Aarsland D, Bronnick K, Alves G, et al. The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease. *J Neurol Neurosurg Ps* 2009; 8:928-930.
36. Starkstein SE, Brockman S. Apathy and Parkinson's disease. *Curr Treat Options Neurol* 2011; 13:267-273.
37. Thobois S, Lhommee E, Klinger H, et al. Parkinsonian apathy responds

- to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain* 2013; 136:1568-1577.
38. Czernecki V, Schupbach M, Yaici S, et al. Apathy following deep brain stimulation in Parkinson's disease: a dopamine responsive symptom. *Movement Disord* 2008; 7:964-969.
 39. Thobois S, Ardouin C, Lhommee E, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain* 2010; 4:1111-1127.
 40. Benito-Leon J, Cubo E, Coronell C, et al. Impact of apathy on health-related quality of life in recently diagnosed Parkinson's disease: the ANIMO study. *Movement Disord* 2012; 2:211-218.
 41. Oguru M, Tachibana H, Toda K, et al. Apathy and depression in Parkinson's disease. *J Geriatr Psych Neur* 2010;1:35-41.
 42. Leroi I, Harbishettar V, Andrews M, et al. Carer burden in apathy and impulse control disorder in Parkinson's disease. *Int J Geriatr Psychiatry* 2012; 27:160-166.
 43. Funkiewiez A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic stimulation on cognitive function, mood and behavior in Parkinson's disease. *J Neurol Neurosurg Ps* 2005;75:834-9.
 44. Saez-Francas N, Hernandez-Vara J, Corominas Rojo M, et al. The association of apathy with central fatigue preception in patients with Parkinson's disease. *Behavioral Neurosci* 2013;127:237-44.
 45. Beiske AG, Svensson E. Fatigue in Parkinson's disease: a short update. *Acta Neurol Scand* 2010;122:78-81.
 46. Pavese N, Metta V, Bose SK, et al. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. *Brain* 2010;133:3434-3443.
 47. Chaudhuri KR, Martinez-Martin P, Antonini P, et al. Rotigotine and specific non-motor symptoms of Parkinson's disease: Post hoc analysis of RECOVER. *Parkinsonism Relat D* 2013;19:660-665.
 48. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex* 2006;7:916-928.
 49. De La Fuente-Fernandez R. Frontostriatal cognitive staging in Parkinson's disease. *Parkinson Dis* 2012; UNSP 561046, doi: 10.1155/2012/561046
 50. Chatterjee A, Fahn S. Methylphenydate treats apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 2002; 14:461-462.
 51. Devos D, Moreau C, Delval A, et al. Methylphenidate a treatment for Parkinson's disease? *CNS Drugs* 2013; 27:1-14.
 52. Mendonca DA, Menezes K, Jog MS. Methylphenidate improves fatigue scores in Parkinson's disease: a randomized controlled trial. *Movement Disord* 2007; 22:2070-2076.
 53. Lhommee E, Klingler H, Thobois S, et al. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours.

- Brain 2012; 135:1463-1477.
54. Martinez-Horta S, Pagonabarraga J, Fernandez de Bobadilla R, et al. Apathy in Parkinson's disease: more than just executive dysfunction. *J Int Neuropsychol Soc* 2013; 19:571-582.
 55. Martinez-Horta S, Riba J, Fernandez de Bobadilla R, et al. Apathy in Parkinson's disease: Neurophysiological evidence of impaired incentive processing. *J Neurosci* 2014; 34:5918-5926.
 56. www.movementdisorders.org/MDS/Education/Rating-Scales.htm [Jun 10 2014]
 57. Antonini A, Abbruzzese G, Ferini-Strambi L, et al. Validation of the Italian version of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale. *Neurol Sci* 2013;34:683-687.
 58. Martinez-Martin P, Rodriguez-Blazquez C, Alvarez-Sanchez M, et al. Expanded and independent validation of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS). *J Neurol* 2013;260:228-236.
 59. Skorvanek M, Kosutzka Z, Valkovic P, et al. [Validation of Slovak version of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)]. *Cesk Slov Neurol N* 2013;76:463-468.
 60. Hurt CS, Landau S, Burn DJ, et al. Cognition, coping, and outcome in Parkinson's disease. *Int Psychogeriatr* 2012; 24:1656-1663.
 61. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease. *Movement Disord* 2011; 26:S42-S80.

Summary

This study focuses on the non-motor symptoms (NMS) of Parkinson's disease (PD), on the tools for their assessment and on the relationships between different NMS in general and Quality of life (QoL). It also focuses on neuropsychiatric symptoms, including fatigue, apathy and depression, which have a high coincidence and can be easily misdiagnosed, on their relationships, their clinical determinants and their relationship to QoL. In the first part of this study we officially validated the Slovak version of the recently published Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in cooperation with the MDS (Chapter 3), and we examined the relationship of the MDS-UPDRS with QoL, with a focus on the non-motor items of the scale (Chapter 4). In the second part of the thesis we studied the associations between selected NMS, including fatigue, apathy and depression and other socio-demographic and clinical variables. Depression represents a major confounder for both fatigue and apathy, as both of these symptoms are part of the DSM-IV criteria for diagnosing depression. Therefore, we separately studied the relationships between depression and fatigue (Chapter 5) and depression and apathy (Chapter 6) and finally the implications that apathy and depression may have on PD-related fatigue (Chapter 7).

Chapter 1 introduced the importance of NMS in PD and further described the variables studied in this thesis. Furthermore, it formulated the basic model of this thesis and posited the five above-indicated research questions.

Chapter 2 provided information about the sample, data sources, measures and statistical analyses used in Chapters 3-7.

Chapter 3 presented the validation of the official Slovak version of the MDS-UPDRS. We found that the overall factor structure of the Slovak version was consistent with that of the English version based on confirmatory factor analyses (CFA) for all four parts of the MDS-UPDRS (all CFI > 0.91). The Slovak scale was confirmed as sharing a common factor structure with the English scale. Therefore, it was designated as the official Slovak version of the MDS-UPDRS. In the exploratory factor analysis, we identified isolated item differences of the factor structure between the Slovak and English versions of the MDS-UPDRS, especially in Part II (motor experiences of daily living).

Chapter 4 explored the relationship between the MDS-UPDRS and QoL, with a focus on the non-motor MDS-UPDRS items. The MDS-UPDRS parts related to worse QoL were part I (non-motor experiences of daily living), part II (motor experiences of daily living) and part IV (motor complications), respectively, but not part III (motor examination).

The PDQ39 summary index score was significantly related to the MDS-UPDRS items Pain, Fatigue and Features of dopamine dysregulation syndrome. Other MDS-UPDRS non-motor items – Depressed mood, Anxious mood, Apathy, Cognitive impairment, Hallucinations and psychosis, Sleep problems, Daytime sleepiness and Urinary problems – were related to some PDQ39 domains, while the MDS-UPDRS items Constipation problems and Light-headedness on standing were not related to any PDQ39 domain.

Chapter 5 explored the proposed concepts of primary fatigue, i.e. fatigue in the absence of a mood disorder and excessive daytime sleepiness (EDS), and of secondary fatigue, i.e. fatigue in the presence of either a mood disorder and/or EDS. Our results show that the clinical determinants of these two types of fatigue differ significantly. Some aspects of the secondary fatigue group were related to older age, male gender, UPDRS part III and anxiety. In the primary fatigue group the only variable significantly associated with MFI reduced activity and mental fatigue domains were BDI-II scores, although within the normality range. Motor symptoms (UPDRS part III) were not associated with any of the MFI domains in the primary fatigue group. Our results show that primary and secondary fatigue can be distinguished and should be considered as separate constructs in future studies.

Chapter 6 explored the clinical determinants of apathy in elderly non-demented PD patients. As shown in our study, apathy and depression can be dissociated in elderly non-demented PD patients, although the coincidence of apathy with depression in our study was higher than reported in previous studies from the general PD population. The most important factors related to apathy in our study were higher depression scores and lower L-dopa equivalent daily dosage (LEDD). Previous studies have reported a correlation between apathy and worse QoL in the PD population. In our study, apathy in a model without depression and anxiety was significantly related to worse QoL; however, when depression and anxiety were added, this relationship was not significant for apathy specifically in the elderly non-demented PD population.

In Chapter 7 we studied the relationship between apathy and fatigue separately in depressed and non-depressed patients, as these had been previously shown to represent different constructs. We found that the prevalence and severity of fatigue and apathy were significantly higher in depressed PD patients. However, our results show that depression, fatigue and apathy can be clearly distinguished in PD, as patients with pure depression, pure apathy and pure fatigue were found in all domains in the study. Apathy was the only clinical determinant of the mental aspects of fatigue in the non-depressed patients in our study, while these were rather related to older age and lower education level in the depressed patients. Apathy was not related to the physical aspects of fatigue in either depressed or non-depressed patients. In this chapter we

furthermore discuss the etiology of both PD-related fatigue and apathy and the potential pathophysiological links between these symptoms.

In Chapter 8 we presented the condensed outcomes of the study, discussed them, argued the strengths and limitations of the study and suggested the implications for both future research as well as clinical settings.

The recently published MDS-UPDRS was designed to address the shortages of the original UPDRS and to become the main outcome measure in PD-related research. This revised MDS-UPDRS particularly covers a wider range of motor as well as non-motor symptoms of PD, and it better differentiates the slight and mild manifestations of the disease. Therefore, it is more suitable for examination of the initial stages of PD and potential trials on disease-modifying treatments. Next, it better describes motor fluctuations, and all individual items have a uniform scoring system. Thanks to the accessible teaching instruments it enables a potentially higher inter-rater reliability. Moreover, the validity and reliability of this scale has been confirmed in multiple other independent studies and in different languages; therefore, we suggest that using MDS-UPDRS in routine clinical practice as well as in research settings is preferable compared with the original UPDRS. Our results also show that the overall burden of NMS in treated PD patients is more important than the motor symptoms, and therefore the NMS should be actively screened and managed.

One of the most important NMS in PD regarding QoL is fatigue, which has been previously associated most commonly with depression. Based on the presence of depression and EDS, we have formulated the concept of primary and secondary fatigue, which presents different constructs in PD; therefore, future studies on the pathophysiology and/or treatment of fatigue should distinguish these concepts in order to prevent sample bias. Moreover, a similar relationship with depression, as seen in fatigue, can also be found in apathy; however, all of these symptoms can be distinguished in PD. As found in our study, apathy is not related to the physical aspects of fatigue in either depressed or non-depressed patients, but we found it to be the only clinical determinant of the mental aspects of fatigue in non-depressed PD patients. It seems that in some of the non-demented and non-depressed PD patients both fatigue and apathy are associated with dopaminergic dysfunctions in the mesolimbic structures and the prefrontal cortex – basal ganglia axis. However, not all PD patients with a hypodopaminergic syndrome develop fatigue or apathy, and their etiology is clearly multifactorial. Therefore, further clinical, neurophysiological as well as imaging studies are needed to better understand the underlying mechanisms and relationships between PD-related fatigue and apathy. From the clinical perspective, optimization of dopaminergic medication as well as an optimal treatment of depression, if present, may lead to improvement of both fatigue and apathy in at least some PD patients.

Samenvatting

Deze studie richt zich op de niet-motorische symptomen (NMS) van de ziekte van Parkinson (PD), op de instrumenten voor de beoordeling ervan en op de relaties tussen de verschillende NMS in het algemeen en kwaliteit van leven (KvL). De studie richt zich ook op neuropsychiatrische symptomen, waaronder vermoeidheid, apathie en depressie, die een aanzienlijke overlap hebben en daardoor gemakkelijk tot een verkeerde diagnose kunnen leiden, op hun onderlinge relaties, hun klinische determinanten en hun relatie tot KvL. In het eerste deel van deze studie hebben we de Slowaakse versie van de onlangs verschenen Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in samenwerking met de MDS officieel gevalideerd (hoofdstuk 3), en onderzochten we de relatie van de MDS UPDRS met KvL, met een focus op de niet-motorische items van de schaal (hoofdstuk 4). In het tweede deel van dit proefschrift hebben we de verbanden tussen geselecteerde NMS, waaronder vermoeidheid, apathie en depressie en andere socio-demografische en klinische variabelen onderzocht. Depressie is een belangrijke verstorende factor voor zowel vermoeidheid en apathie, omdat beide symptomen deel uitmaken van de DSM-IV criteria voor de diagnose van depressie. Daarom bestudeerden we afzonderlijk de relatie tussen depressie als vermoeidheid (hoofdstuk 5) en depressie en apathie (hoofdstuk 6) en tenslotte de implicaties die apathie en depressie kunnen hebben op de PD-gerelateerde vermoeidheid (hoofdstuk 7).

In Hoofdstuk 1 werd het belang van de NMS bij PD en de verder beschreven variabelen die in dit proefschrift bestudeerd zijn, geïntroduceerd. Bovendien werd het basismodel van dit proefschrift geformuleerd en de vijf hierboven vermelde onderzoeksvragen geponeerd.

In Hoofdstuk 2 wordt informatie gegeven over de steekproef, de gegevensbronnen, meetinstrumenten en statistische analyses die gebruikt worden in de hoofdstukken 3-7.

In Hoofdstuk 3 wordt de validatie van de officiële Slowaakse versie van de MDS-UPDRS gepresenteerd. We vonden dat de totale factorstructuur van de Slowaakse versie in overeenstemming was met die van de Engelse versie gebaseerd op confirmatieve factor analyse (CFA) voor alle vier de onderdelen van de MDS-UPDRS (alle CFI > 0,91). Deze uitkomst leidde tot de conclusie dat de Slowaakse schaal eenzelfde factorstructuur had als de Engelse schaal. Daarom werd deze schaal aangewezen als de officiële Slowaakse versie van de MDS-UPDRS. In de exploratieve factoranalyse vonden we geïsoleerde item verschillen in de factorstructuur tussen de Slowaakse en de Engels versie van de MDS-UPDRS, vooral in Deel II, de motorische ervaringen van het dagelijkse leven.

In Hoofdstuk 4 werd de relatie tussen de MDS-UPDRS en QoL onderzocht, met een focus op de niet-motorische MDS-UPDRS items. De MDS-UPDRS delen met betrekking tot slechtere kwaliteit van leven waren deel I (niet-motorische ervaringen van het dagelijkse leven), deel II (motorische ervaringen van het dagelijkse leven) en deel IV (motorische complicaties), maar niet deel III (motorisch onderzoek). De totale PDQ39 was significant gerelateerd aan de MDS-UPDRS items pijn, vermoeidheid en kenmerken van dopamine dysregulatie syndroom. Andere MDS-UPDRS niet-motorische items - depressieve stemming, angstige stemming, apathie, cognitieve stoornissen, hallucinaties en psychose, slaapproblemen, slaperigheid overdag en plasproblemen - waren gerelateerd aan een aantal PDQ39 domeinen, terwijl de MDS-UPDRS items constipatie problemen en het gevoel van licht in het hoofd bij het opstaan niet gerelateerd waren aan een PDQ39 domein.

In Hoofdstuk 5 werden de voorgestelde concepten primaire vermoeidheid - zonder dat er sprake van een stemmingsstoornis en overmatige slaperigheid overdag (EDS) - en secundaire vermoeidheid - moeheid in aanwezigheid van hetzij een stemmingsstoornis en / of EDS - onderzocht. Onze resultaten laten zien dat de klinische determinanten van deze twee soorten vermoeidheid significant verschillen. Sommige aspecten van de secundaire vermoeidheidsgroep waren gerelateerd aan een hogere leeftijd, mannelijk geslacht, UPDRS deel III en angst. In de primaire vermoeidheid groep waren de enige variabelen die significant geassocieerd waren met de MFI verminderde activiteit en mentale vermoeidheid domeinen de scores van de BDI-II, maar die vielen binnen de normale range. Motorische symptomen (UPDRS Deel III) waren niet geassocieerd met een van de MFI-domeinen in de groep met primaire vermoeidheid. Onze resultaten tonen aan dat primaire en secundaire vermoeidheid te onderscheiden entiteiten zijn en als afzonderlijke constructen in toekomstige studies moeten worden beschouwd.

In Hoofdstuk 6 werden de klinische determinanten van apathie bij oudere niet-demente PD-patiënten onderzocht. Zoals aangetoond in ons onderzoek, kunnen apathie en depressie worden onderscheiden bij oudere niet-demente PD patiënten, maar de overlap tussen apathie met depressie kwam daar vaker voor dan in eerder onderzoek onder de algemene bevolking met PD. De belangrijkste factoren die in onze studie gerelateerd zijn aan apathie waren hogere depressiescores en een lagere L-dopa equivalente dagelijkse dosering (LEDD). In eerder onderzoek is een correlatie tussen apathie en een slechtere kwaliteit van leven bij de PD bevolking gevonden. In onze studie was apathie in een model zonder depressie en angst significant gerelateerd aan een slechtere kwaliteit van leven; echter, wanneer depressie en angst werden toegevoegd, bleek deze relatie niet langer significant voor apathie, in het bijzonder bij de oudere niet-demente PD populatie.

In hoofdstuk 7 onderzochten we het verband tussen apathie en vermoeidheid afzonderlijk bij depressieve en niet-depressieve patiënten, aangezien eerder was aangetoond dat het hier verschillende constructen betrof. We vonden dat de prevalentie en de ernst van vermoeidheid en apathie significant hoger waren bij depressieve PD patiënten. Echter, in onze studie vonden we patiënten met pure depressie, pure apathie en pure vermoeidheid, hetgeen suggereert dat al deze symptomen bij PD van elkaar kunnen worden onderscheiden. Apathie was de enige klinische determinant van de mentale aspecten van vermoeidheid bij de niet-depressieve patiënten in ons onderzoek. Mentale aspecten van vermoeidheid bij depressieve patiënten bleek verband te houden met een oudere leeftijd en het lager onderwijs. Apathie was niet gerelateerd aan de fysieke aspecten van vermoeidheid in depressieve en niet-depressieve patiënten. In dit hoofdstuk wordt verder de etiologie van zowel PD-gerelateerde vermoeidheid als apathie en de mogelijke pathofysiologische

In hoofdstuk 8 presenteerden we de verkorte uitkomsten van de studie, bediscussieerden ze, gingen in op de sterkte kanten en de beperkingen van het onderzoek en kwamen met implicaties voor zowel toekomstig onderzoek als voor de klinische praktijk.

De recent gepubliceerde MDS-UPDRS is ontworpen om de tekorten van de oorspronkelijke UPDRS te compenseren en de belangrijkste uitkomstmaat in PD-gerelateerde onderzoek te worden. Deze herziene MDS-UPDRS omvat in het bijzonder een groter aantal motorische en niet-motorische symptomen van PD, en onderscheidt beter de lichte en milde ziekteverschijnselen. Daarom is dit instrument meer geschikt voor het onderzoek van de eerste stadia van PD en voor potentiële proeven met ziekte-modificerende behandelingen. Vervolgens beschrijft het beter de motorische fluctuaties, met voor alle individuele items een uniform scoringsysteem. De toegankelijke trainingsinstrumenten dragen bij tot een potentieel hogere interbeoordelaars betrouwbaarheid. Bovendien is de validiteit en betrouwbaarheid van deze schaal nagegaan in meerdere onafhankelijke studies en in verschillende talen; daarom suggereren we dat het gebruik van MDS-UPDRS in de routine klinische praktijk als in de onderzoeksinstellingen de voorkeur geniet boven de oorspronkelijke UPDRS. Onze resultaten tonen ook aan dat de totale lasten van de NMS bij behandelde PD-patiënten belangrijker is dan de motorische symptomen, en dus de NMS actief moeten worden gescreend en behandeld.

Een van de belangrijkste NMS bij PD met betrekking tot QoL is vermoeidheid, dat eerder meestal geassocieerd werd met depressie. Gebaseerd op de aanwezigheid van depressie en EDS hebben we groepen met primaire en secundaire vermoeidheid onderscheiden, die verschillende constructen in PD weergeven. Derhalve zouden toekomstige studies naar de pathofysiologie en / of behandeling van vermoeidheid deze concepten moeten onderscheiden teneinde

een vertekening van de steekproef te voorkomen. Bovendien kan een soortgelijke relatie als tussen depressie en vermoeidheid ook worden gevonden in apathie; echter al deze symptomen zijn te onderscheiden bij PD. Uit ons onderzoek blijkt dat apathie niet is gerelateerd aan de fysieke aspecten van vermoeidheid, zowel bij depressieve als bij niet-depressieve patiënten, maar wel dat het de enige klinische determinant was van de mentale aspecten van vermoeidheid bij niet-depressieve PD patiënten. Het lijkt erop dat bij sommige van de niet-demente en niet-depressieve PD patiënten zowel vermoeidheid als apathie geassocieerd is met dopaminerge disfuncties in de mesolimbische structuren en de prefrontale cortex - basale ganglia as. Echter, niet alle PD patiënten die een hypodopaminergisch syndroom krijgen ontwikkelen vermoeidheid of apathie en de etiologie ervan is duidelijk multifactorieel. Daarom zijn verdere klinische, neurofysiologische en beeldvormende studies nodig om een beter inzicht te verwerven in de onderliggende mechanismen en relaties tussen PD-gerelateerde vermoeidheid en apathie. Vanuit een klinisch perspectief kan optimalisatie van dopaminerge medicatie, alsook een optimale behandeling van depressie, indien aanwezig, leiden tot verbetering van zowel vermoeidheid als apathie in bij een belangrijk deel van de PD patiënten.

Zhrnutie

Táto práca je zameraná na nemotorické symptómy (NMS) Parkinsonovej choroby (PCh), na možnosti ich diagnostikovania a vzťah medzi jednotlivými NMS a kvalitou života. Takisto sa zameriava na neuropsychiatrické symptómy vrátane únavy, apatie a depresie, ktoré môžu mať vysokú koincidenciu a môžu byť ľahko zamenené, na ich klinické determinanty a ich vzťah ku kvalite života (QoL). V prvej časti tejto práce sme v spolupráci s International Parkinson and Movement Disorder Society (IPMDS) oficiálne validizovali slovenskú verziu nedávno publikovanej škály Movement-Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (kapitola 3) a skúmali sme vzťah škály MDS-UPDRS ku kvalite života s bližším zameraním na nemotorické položky škály (kapitola 4). V druhej časti práce sme skúmali asociácie medzi vybranými NMS, vrátane únavy, apatie a depresie, a inými socio-demografickými a klinickými premennými. Depresia predstavuje najvýznamnejší mätúci faktor pri hodnotení únavy aj apatie, nakoľko sú obidva tieto symptómy súčasťou DSM-IV kritérií pre diagnózu depresie. Preto sme študovali osobitne vzťahy medzi únavou a depresiou (kapitola 5), apatiou a depresiou (kapitola 6) a v poslednom rade možný dopad apatie a depresie na únavu asociovanú s PCh (kapitola 7).

V kapitole 1 je načrtnutý význam NMS pri PCh a sú bližšie popísané premenné skúmané v tejto práci. Navyše je v tejto kapitole sformulovaný základný výskumný model práce a päť výskumných otázok.

Kapitola 2 poskytuje informácie o výskumnej vzorke, metodike a štatistickej analýze použitej v kapitolách 3-7.

Kapitola 3 prezentuje validizáciu oficiálnej slovenskej verzie škály MDS-UPDRS. Zistili sme, že faktorová štruktúra slovenskej verzie je na základe konfirmačnej faktorovej analýzy pre všetky štyri časti MDS-UPDRS (všetky CFI>0,91) konzistentná s pôvodnou anglickou verziou. Slovenská verzia škály zdieľa spoločnú faktorovú štruktúru s anglickou verziou, na základe čoho bola uznaná za oficiálny slovenský preklad MDS-UPDRS. V rámci exploračnej faktorovej analýzy sme identifikovali izolované rozdiely vo faktorovej štruktúre medzi jednotlivými položkami slovenskej a anglickej verzie MDS-UPDRS, predovšetkým v časti II (motorické skúsenosti denného života).

V kapitole 4 je bližšie skúmaný vzťah medzi MDS-UPDRS a kvalitou života so zameraním na nemotorické položky MDS-UPDRS. Časti MDS-UPDRS asociované s horšou kvalitou života boli časť I (nemotorické skúsenosti denného života), časť II (motorické skúsenosti denného života) a časť IV (motorické komplikácie) avšak tento vzťah nebol zistený pre časť III (vyšetrenie motoriky). PDQ39 summary index bol signifikantne

asociovaný s MDS-UPDRS položkami Bolest, Únava a Prejavy syndrómu dopamínovej dysregulácie. Iné nemotorické položky MDS-UPDRS – Depresívna nálada, Úzkostná nálada, Apatia, Zhoršenie kognitívnych funkcií, Halucinácie a psychóza, Denná spavosť, Problémy so spánkom a Problémy s močením boli asociované len s niektorými doménami PDQ39. Položky Problémy so stolicou a Závrativosť pri zmene polohy tela neboli asociované so žiadnou doménou PDQ39.

Kapitola 5 skúma navrhované koncepty primárnej únavy, t.j. únavy v neprítomnosti poruchy nálady a nadmernej dennej spavosti (EDS), a sekundárnej únavy, t.j. únavy v koincidencii s poruchou nálady alebo EDS. Naše výsledky ukazujú, že klinické determinanty týchto dvoch typov únavy sa významne líšia. Niektoré aspekty sekundárnej únavy boli asociované s vyšším vekom, mužským pohlavím, UPDRS časťou III a úzkosťou. V skupine s primárnou únavou boli vyššie skóre BDI-II (aj keď v hladine normality) jedinou premennou asociovanou s MFI doménami znížená aktivita a mentálna únava. Motorické prejavy (UPDRS časť III) neboli v skupine s primárnou únavou asociované so žiadnymi doménami MFI. Naše výsledky ukazujú, že primárna a sekundárna únava môžu byť rozlíšené, a preto by mali byť v budúcich štúdiách hodnotené ako osobitné konštrukty.

Kapitola 6 skúmala klinické determinanty apatie v geriatrickej populácii pacientov s PCh. Naše výsledky ukazujú, že apatia a únava môžu byť v tejto populácii rozlíšené, aj keď apatia v koincidencii s depresiou bola v našej štúdií prítomná častejšie ako bolo popisované v iných štúdiách realizovaných na celkovej populácii pacientov s PCh. Najvýznamnejšími premennými asociovanými s apatiou boli v našej štúdií vyššie skóre depresie a nižšia hladina denného ekvivalentu levodopy (LEDD). V predchádzajúcich štúdiách u pacientov s Parkinsonovou chorobou bol demonštrovaný vzťah medzi apatiou a horšou kvalitou života. V našej štúdií bola apatia v modeli bez depresie a anxiety signifikantne asociovaná s horšou kvalitou života; po pridaní depresie a anxiety do modelu však tento vzťah špecificky v geriatrickej populácii pacientov s PCh nebol signifikantný.

V kapitole 7 sme študovali vzťah medzi apatiou a únavou osobitne u pacientov s depresiou a bez depresie. Zistili sme, že prevalencia a závažnosť únavy a apatie boli významne vyššie u depresívnych pacientov s PCh. Naše výsledky však ukazujú, že depresia, únava a apatia môžu byť pri PCh jednoznačne odlišné, keďže sme identifikovali pacientov s čistou depresiou, čistou apatiou a čistou únavou vo všetkých doménach. Apatia bola jediným determinantom mentálnych aspektov únavy u nedepratívnych pacientov, zatiaľ čo tieto boli u depresívnych pacientov asociované skôr s vyšším vekom a nižším vzdelaním. Apatia nebola asociovaná s fyzickými aspektami únavy, tak u depresívnych, ako aj u nedepratívnych pacientov. V tejto kapitole navyše diskutujeme

o etiológii únavy a apatie viazaných na PCh a potenciálnych patofyziologických spojivách medzi týmito symptómami.

V kapitole 8 prezentujeme kondenzované výsledky štúdie, diskutujeme ich, prezentujeme silné stránky a limitácie práce a navrhujeme implikácie pre budúci výskum ako aj klinickú prax.

Nedávno publikovaná škála MDS-UPDRS bola zostrojená za účelom adresovania nedostatkov pôvodnej škály UPDRS a s cieľom vytvoriť hlavný klinický nástroj vo výskume PCh. Revidovaná verzia MDS-UPDRS pokrýva predovšetkým väčšie spektrum motorických ako aj nemotorických prejavov PCh, lepšie diferencuje nepatrné a mierne prejavy ochorenia. Je preto vhodnejšia pre vyšetovanie včasných štádií PCh a používanie v štúdiách s potenciálne ochorenie-modifikujúcimi liekmi. MDS-UPDRS navyše lepšie popisuje motorické fluktuácie a všetky položky majú uniformné skóvanie. Vzhľadom na dostupné výučbové materiály a moduly tiež umožňuje potenciálne vyššiu zhodu medzi rôznymi hodnotiteľmi. Validita a reliabilita škály bola potvrdená vo viacerých nezávislých štúdiách a v rôznych jazykoch. Preto si myslíme, že používanie MDS-UPDRS v bežnej rutinnej praxi ako aj vo výskume je vhodnejšie ako používanie pôvodnej verzie UPDRS. Naše výsledky ukazujú, že celkové bremeno nemotorických prejavov u liečených pacientov s PCh je významnejšie ako motorických prejavov, a preto by mali byť NMS aktívne vyhľadávané a manažované.

V zmysle kvality života je jedným z najvýznamnejších NMS pri PCh únava, ktorá bola v minulosti často asociovaná s depresiou. Na základe prítomnosti depresie a EDS sme formulovali koncept primárnej a sekundárnej únavy, ktoré predstavujú osobitné konštrukty; budúce štúdie týkajúce sa patofyziológie a/alebo liečby únavy, by preto mali tieto koncepty odlišovať, aby sa vyhli chybám pri ich vyhodnocovaní. Navyše, pri apatii nachádzame podobný vzťah s depresiou ako pri únave; všetky tieto prejavy však môžu byť pri PCh odlišené. V našej štúdii sme zistili, že apatia nie je asociovaná s fyzickou únavou u depresívnych ani u nedeprívnych pacientov, avšak zistili sme, že je jediným determinantom mentálnej únavy u nedeprívnych pacientov. Zdá sa, že u niektorých pacientov bez demencie a bez depresie sú únava aj apatia asociované s dopaminergnou dysfunkciou v mesolimbických štruktúrach a dysfunkciou osi prefrontálny kortex – bazálne gangliá. Únava a apatia však nevzniknú u všetkých pacientov s hypodopaminergným syndrómom a ich etiológia je zjavne multifaktoriálna. Za účelom lepšieho porozumenia podmieňujúcich mechanizmov a vzťahu apatie a únavy pri PCh sú potrebné ďalšie klinické ako aj neurofyziologické štúdie. Z klinického hľadiska môže viesť k zmierneniu apatie aj únavy u časti pacientov s PCh jednak optimalizácia dopaminergnej liečby ako aj adekvátna liečba depresie.

Acknowledgments

It is my great pleasure to have a chance and thank all those who have contributed to this thesis.

First of all, my deep gratitude goes to all patients who have agreed to participate in this research project. Without their contribution, this work wouldn't be possible.

From *University Medical Center Groningen, the Netherlands* my special thanks goes to my co-promotor Assoc. prof. *Jitse P. van Dijk*, from whom I have learned a lot in terms of planning and performing scientific research and about the principles of writing. His regular visits to Slovakia and involvement in my thesis pushed me always to work harder and keep up with the expectations.

My sincere appreciation goes also to my promotor *Prof. Dr. Johan W. Groothoff* for his support, as well as stimulating remarks and ideas on improving the manuscripts.

My special gratitude belongs to the members of the Promotion Board, namely *Prof. Dr. P. de Deyn, Prof. Dr. M.A.J. de Koning-Tijssen and Prof. Dr. S.A. Reijneveld* from UMCG, Groningen, Netherlands and *Prof. Dr. J. Roth* from Charles University in Prague, Czech Republic for their stimulating comments and discussion.

From Slovakia my thanks goes in first place especially to my promotor, head of our department and mentor in the field of neurology in one person *Prof. Dr. Zuzana Gdovinova*. I am very thankful for all her practical and ongoing support and trust in my research and clinical ideas.

My thanks belong also to all colleagues from our department as well as other colleagues from the Medical Faculty of Safarik University in Kosice and University of Hospital of L. Pasteur in Kosice for their support and stimulating cooperation.

My deep gratitude goes to my co-promotor *Dr. Jaroslav Rosenberger* and to *Dr. Iveta Rajnicova-Nagyova* for their lessons in statistics and methodology, as well as for their stimulating comments on the manuscripts. My thanks belongs also to *Radka Ghorbani Saeedian* and *Dr. Martina Krokavcova*, who were very helpful during the initiation of this project. My thanks belong also to my research assistants *Cecilia Bukatova, Dominika Lazurova* and *Maria Anna Ficikova* who were very helpful during the gathering and administration of research data. My appreciation belongs also to *David L. McLean* for his English language proofreading.

My great appreciation belongs to other co-authors of my manuscripts - Slovak colleagues working in the field of Movement Disorders and participating in this project, namely *Assoc. prof. Dr. Peter Valkovic* and his

colleagues *Dr. Michal Minar* and *Dr. Zuzana Kosutzka* from the 2nd Dept. of Neurology, Comenius University in Bratislava and to *Dr. Milan Grofik* from the Dept. of Neurology, Comenius University in Martin.

My thanks belongs also to *Prof. Dr. Christopher G. Goetz*, *Prof. Dr. Glenn T. Stebbins*, *Prof. Dr. Barbara C. Tilley* and *Dr. Jing Huang* from the International Parkinson and Movement Disorder Society for the waiver of the administration fee for validation of the Slovak version of the MDS-UPDRS scale and for their stimulating cooperation in this project.

My gratitude goes also to colleagues from the Movement Disorders Center, Charles University in Prague, Czech Republic, especially *Prof. Dr. Evzen Ruzicka*, *Prof. Dr. Jan Roth* and *Prof. Dr. Robert Jech* and also to colleagues from the Unit of Functional Neurosurgery, NHNN, Queens Square, London, UK, especially to *Dr. Tom Foltynie* and *Prof. Dr. Patricia Limousin* where I have spent time during my study stays. Wonderful time spent in your departments was very fruitful for me and helped me to improve greatly my clinical and research skills in the field of Movement Disorders and Deep Brain Stimulation.

My special appreciation goes to both of my parents who brought me to science in first place and are a big example for me in life.

Last, but not least my great thanks goes to my wife *Helena* and our children for their love, patience and support, it means the whole world to me.

Matej Skorvanek

October 2014

About the author

Matej Skorvanek was born on April 30th 1984 in Kosice, Slovakia. After studying the grammar schools in Kosice Slovakia, in Lüttau, Germany and in Newton, MA, USA, he completed the high school in Kosice and started to study at the Medical Faculty of P. J. Safarik University in Kosice, where he graduated in July 2008 as a medical doctor (MD).

Since September 2008 he worked as a neurologist at the Dept. of Neurology in University Hospital of L. Pasteur in Kosice and since October 2010 he moved to a position of lecturer at the Dept. of Neurology, Medical Faculty of P. J. Safarik University in Kosice. In October 2013 he passed his specialization exam in neurology and wrote a thesis "Dystonia and dystonic syndromes". During this period and during his training in the field of Movement Disorders he cooperated and attended study stays at the 1st Department of Neurology, Charles University in Prague, Czech republic for 3 weeks in year 2011 (Prof. Ruzicka, Prof. Roth, Prof. Jech) and at the Unit of Functional Neurosurgery, UCL Institute of Neurology, NHNN, Queens square 33, London, UK for 6 weeks in year 2012 (Dr. Foltynie, Prof. Limousin). Later he initiated and now is in charge of the DBS program in the University Hospital of L. Pasteur in Kosice.

His professional interest in PD research was mostly in non-motor PD symptoms, especially fatigue and apathy. He is the Slovak principal investigator and coordinator for the validation of Slovak versions of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the Unified Dyskinesia Rating Scale. He is a member of the Movement Disorder Society Task Force on the Development of the MDS-UPDRS and coordinator of a large international multicenter study assessing the relationship between the MDS-UPDRS and different quality of life measures. He is also coordinator of a prospective study evaluating alpha-synuclein in colonic biopsies as a potential tissue biomarker of premotor Parkinson's disease. Furthermore, his research interest lies also in the field of dystonia and he is a Management Committee member of the COST action BM1101 "European network for the study of dystonia syndrome". He is also one of the founding members and initiators of the Movement Disorders section of the Slovak Neurological Society.

Graduate School Kosice Institute for Society and Health (KISH) and previous dissertations

The Graduate School Kosice Institute for Society and Health (KISH) was established in 2004. The Graduate School KISH is hosted by the Medical Faculty of Pavol Jozef Safarik University in Kosice (Slovakia). KISH researchers originate from the Medical Faculty, the University Hospital and other hospitals, and the Faculty of Arts. Its research concentrates on public health, health psychology, epidemiology and medical sociology. The interdisciplinary research programs focus on **Chronic Disease** and **Youth and Health**.

The Graduate School KISH is collaborating closely with the Division of Community and Occupational Medicine, University Medical Center Groningen, University of Groningen, The Netherlands.

Previous dissertations from the Graduate School KISH

Prihodova L (2014) *Psychosocial and medical determinants of long-term patient outcomes*.

Supervisor: Prog. Dr. JW Groothoff

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Rajnicova-Nagyova, Dr. J Rosenberger

<http://irs.ub.rug.nl/ppn/381201090>

Behanova M (2014) *Area- and individual-level socioeconomic differences in health and health-risk behaviours. A comparison of Slovak and Dutch cities*

Supervisor: Prof. Dr. SA Reijneveld

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Rajnicova-Nagyova, Dr. Z Katreniakova

<http://irs.ub.rug.nl/ppn/375806504>

Silarova B (2014) *Unraveling the role of sense of coherence in coronary heart disease patients*

Supervisor: Prof. Dr. SA Reijneveld

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Nagyova

<http://irs.ub.rug.nl/ppn/371319919>

Pitel L (2013) *Sociocultural determinants, gender and health-related behaviour in adolescence*

Supervisor: Prof. Dr. SA Reijneveld

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. A Madarasova Geckova

<http://irs.ub.rug.nl/ppn/369599624>

Majernikova M (2013) *Self-rated health and mortality after kidney transplantation*

Supervisor: Prof. Dr. JW Groothoff

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. J Rosenberger, Dr. R Roland

<http://irs.ub.rug.nl/ppn/369598342>

Bobakova D (2013) *Youth subcultures and problem behaviours in Slovakia: Hip-Hop, Techno-Scene, metal, Punk, Skinheads and Roma*

Supervisor: Prof. Dr. SA Reijneveld

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. A Madarasova Geckova

<http://irs.ub.rug.nl/ppn/357978870>

Rosicova K (2013) *Regional mortality in Slovakia: Socioeconomic indicators and ethnicity*

Supervisor: Prof. Dr. JW Groothoff

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. A Madarasova Geckova

<http://irs.ub.rug.nl/ppn/357966791>

Benka J (2012) *Living with Rheumatoid Arthritis: Do personal and social resources make a difference?*

Supervisors: Prof. Dr. JW Groothoff, Prof. Dr. JJJ van der Klink

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Nagyova

<http://irs.ub.rug.nl/ppn/354811118>

Kalina O (2012) *Sexual risky behavior among Slovak adolescents and young adults: Social and psychological factors*

Supervisor: Prof. Dr. SA Reijneveld

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. A Madarasova Geckova

<http://irs.ub.rug.nl/ppn/353218561>

- Salonna F (2012) *Health inequalities among Slovak adolescents over time*
 Supervisors: Prof. Dr. SA Reijneveld, Prof. Dr. JW Groothoff
 Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. A Madarasova Geckova
<http://irs.ub.rug.nl/ppn/345879597>
- Kolarcik P (2012) *Self-reported health and health risky behaviour of Roma adolescents in Slovakia. A comparison with the non-Roma*
 Supervisor: Prof. Dr. SA Reijneveld
 Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. A Madarasova Geckova
<http://irs.ub.rug.nl/ppn/345878396>
- Tomcikova Z (2011) *Parental divorce and adolescent excessive drinking: Role of parent-adolescent relationship and other social and psychosocial factors*
 Supervisor: Prof. Dr. SA Reijneveld
 Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. A Madarasova Geckova
<http://irs.ub.rug.nl/ppn/332352617>
- Veselska Z (2010) *Perception of self and health-related behavior in adolescence*
 Supervisor: Prof. Dr. SA Reijneveld
 Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. A Madarasova Geckova
<http://irs.ub.rug.nl/ppn/330592696>
- Dubayova T (2010) *Parkinson's disease – psychological determinants of quality of life*
 Supervisor: Prof. Dr. JW Groothoff
 Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Nagyova, Assoc. Prof. Dr. Z Gdovinova, dr. LJMiddel
<http://irs.ub.rug.nl/ppn/330630423>
- Sarkova M (2010) *Psychological well-being and self-esteem in Slovak adolescents*
 Supervisor: Prof. Dr. WJA van den Heuvel
 Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. Z Katreniakova, Assoc. Prof. A Madarasova- Geckova
<http://irs.ub.rug.nl/ppn/330592173>
- Krokavcova M (2009) *Perceived Health Status in multiple sclerosis patients*
 Supervisor: Prof. Dr. JW Groothoff

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Nagyova, Assoc.
Prof. Z Gdovinova, Dr. LJ Middel
<http://irs.ub.rug.nl/ppn/318259753>

Havlikova E (2008) *Fatigue, mood disorders and sleep problems in patients with Parkinson's disease*

Supervisor: Prof. Dr. JW Groothoff

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. J Rosenberger,
Assoc. Prof. Z Gdovinova, Dr. LJ Middel

<http://irs.ub.rug.nl/ppn/315252448>

Skodova Z (2008) *Coronary heart disease from a psychosocial perspective: Socioeconomic and ethnic inequalities among Slovak patients*

Supervisor: Prof. Dr. SA Reijneveld

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Nagyova, Dr. LJ
Middel, Dr. M Studencan

<http://irs.ub.rug.nl/ppn/31539823X>

Rosenberger J (2006) *Perceived health status after kidney transplantation*

Supervisors: Prof. Dr. JW Groothoff, Prof. Dr. WJA van den Heuvel

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. R Roland

<http://irs.ub.rug.nl/ppn/297874527>

Sleskova M (2006) *Unemployment and the health of Slovak adolescents*

Supervisors: Prof. Dr. SA Reijneveld, Prof. Dr. JW Groothoff

Co-Supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. A
Madarasova Geckova

<http://irs.ub.rug.nl/ppn/297872109>

Nagyova I (2005) *Self-rated health and quality of life in Slovak rheumatoid arthritis patients*

Supervisor: Prof. Dr. WJA van den Heuvel

Co-Supervisor: Assoc. Prof. Dr. JP van Dijk

<http://irs.ub.rug.nl/ppn/274118556>

Geckova A (2002) *Inequality in health among Slovak adolescents*

Supervisors: Prof. Dr. D Post, Prof. Dr. JW Groothoff

Co-Supervisor: Assoc. Prof. Dr. JP van Dijk

<http://irs.ub.rug.nl/ppn/236175823>

Groningen Graduate School of Medical Sciences – Research Institute SHARE and previous dissertations

This thesis is published within the **Research Institute SHARE** (Science in Healthy Ageing and Health caRE) of the University Medical Center Groningen / University of Groningen.

Further information regarding the institute and its research can be obtained from our internet site: www.share.umcg.nl

More recent theses can be found in the list below.

((co-) supervisors are between brackets)

2014

Beijers CGHM

Unhealthy behaviors during pregnancy; who continues to smoke and consume alcohol, and is treatment of anxiety and depressive symptoms effective?

(prof J Ormel, prof CLH Bockting, dr H Burger)

Kerdijk W

Strategic choices in curriculum design to facilitate knowledge and competency development

(prof J Cohen-Schotanus, prof JW Snoek, dr R Tio)

Spaans F

Hemopexin activity and extracellular ATP in the pathogenesis of preeclampsia

(prof H van Goor, dr MM Faas, dr WW Bakker)

Brinksma A

Nutritional status in children with cancer

(prof PF Roodbol, prof R Sanderman, prof ESJM de Bont, dr WJE Tissing)

Prihodova L

Psychological and medical determinants of long-term patient outcomes; a specific focus on patients after kidney transplantation and with haemophilia

(prof JW Groothoff, dr JP van Dijk, dr I Rajnicova-Nagyova, dr J Rosenberger)

Snippe E

Understanding change in psychological treatments for depressive symptoms; the individual matters

(prof R Sanderman, prof PMG Emmelkamp, dr MJ Schroevers, dr J Fleer)

Groen B

Complications in diabetic pregnancy; role of immunology and Advanced Glycation End products

(prof TP Links, prof PP van den Berg, dr MM Faas)

Visser L

Early detection and prevention of adolescent alcohol use; parenting and psychosocial factors

(prof SA Reijneveld, dr AF de Winter)

Tovote KA

Acceptance or challenge? Psychological treatments for depressive symptoms in patients with diabetes

(prof R Sanderman, prof PMG Emmelkamp, prof TP Links)

Trippolini M

Evaluation of functioning in workers with whiplash-associated disorders and back pain

(prof MF Reneman, prof PU Dijkstra, prof JHB Geertzen)

Eriks-Hoogland IE

Shoulder impairment in persons with a spinal cord injury & associations with activities and participation

(prof LHV van der Woude, prof G Stucki, prof MWM Post, dr S de Groot)

Suwantika AA

Economic evaluations of non-traditional vaccinations in middle-income countries: Indonesia as a reference case

(prof MJ Postma, dr K Lestari)

Behanova M

Area- and individual-level socioeconomic differences in health and health-risk behaviours; a comparison of Slovak and Dutch cities

(prof SA Reijneveld, dr JP van Dijk, dr I Rajnicova-Nagyova, dr Z Katreniakova)

Dekker H

Teaching and learning professionalism in medical education

(prof J Cohen-Schotanus, prof T van der Molen, prof JW Snoek)

Dontje ML

Daily physical activity in patients with a chronic disease

(prof CP van der Schans, prof RP Stolk)

Gefenaite G

Newly introduced vaccines; effectiveness and determinants of acceptance

(prof E Hak, prof RP Stolk)

Dagan M

The role of spousal supportive behaviors in couples' adaptation to colorectal cancer

(prof M Hagedoorn, prof R Sanderman)

Monteiro SP

Driving-impairing medicines and traffic safety; patients' perspectives

(prof JJ de Gier, dr L van Dijk)

Bredeweg S

Running related injuries

(prof JHB Geertzen, dr J Zwerver)

Mahmood SI

Selection of medical students and their specialty choices

(prof JCC Borleffs, dr RA Tio)

Kriekke JAJ van der

Patients' in the driver's seat; a role for e-mental health?

(prof P de Jonge, prof M Aiello, dr S Sytma, dr A Wunderink)

Jong LD de

Contractures and hypertonia of the arm after stroke; development, assessment and treatment

(prof K Postema, prof PU Dijkstra)

Tiessen AH

Cardiovascular risk management in general practice

(prof K van der Meer, prof AJ Smit, dr J Broer)

Bodde MI

Complex Regional Pain Syndrome type 1 & amputation

(prof JHB Geertzen, prof PU Dijkstra, dr WFA van der Dunnen)

Lakke AE

Work capacity of patients with chronic musculoskeletal pain

(prof JHB Geertzen, prof MF Reneman, prof CP van der Schans)

Silarova B

Unraveling the role of sense of coherence in coronary heart disease patients

(prof SA Reijneveld, dr JP van Dijk, dr I Rajnicova-Nagyova)

Weening-Dijksterhuis E

Physical exercise to improve or maintain Activities of Daily Living performance in frail institutionalized older persons

(prof CP van der Schans, prof JPJ Slaets, dr MHG de Greef, dr W Krijnen)

Koolhaas W

Sustainable employability of ageing workers; the development of an intervention

(prof JJL van der Klink, prof JW Groothoff, dr S Brouwer)

Flach PA

Sick leave management beyond return to work

(prof JW Groothoff, prof U Bültmann)

For 2013 and earlier theses visit our website

ISBN: 978-90-367-7490-1