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## **Pituitary diseases : long-term psychological consequences**

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# Chapter 9

## General discussion and summary



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## 1. Introduction

In the present thesis, we explored the long-term consequences of pituitary diseases from a psychological perspective. Pituitary and adrenal adenomas can be treated quite adequately from a medical perspective, but these patients suffer from impaired quality of life (QoL) despite long-term remission or cure. This decreased QoL is assumed to originate mostly from physical complaints, but psychological problems might also contribute.

## 2. Illness perceptions

Although decreased QoL may originate from persisting limitations due to irreversible effects of previous excessive hormone exposure, an alternative hypothesis is that the psychological impact of suffering from this disease reduces QoL. The aim of the study described in **Chapter 2** was to explore the illness perceptions of patients after long-term remission of Cushing's syndrome. This is the first time that illness perceptions are addressed in endocrine diseases in general. We used several validated QoL questionnaires and the Illness Perception Questionnaire Revised to assess QoL and illness perceptions. The results indicate that affected illness perceptions and reduced QoL parameters are strongly related. Moreover, patients after long-term remission of Cushing's syndrome reported more negative illness perceptions compared with several reference groups with acute and chronic conditions. In addition, patients with hydrocortisone dependency had stronger beliefs regarding the chronic nature and the cyclical nature of Cushing's syndrome than patients without hydrocortisone dependency. Furthermore, hypopituitarism was associated with the number of symptoms attributed to Cushing's syndrome, chronicity and fluctuations of the disease, and the perceived consequences of Cushing's syndrome. Therefore, hydrocortisone dependency and hypopituitarism both influence illness perceptions.

The perceptions of patients depend on information from different sources. Therefore, these illness perceptions do not necessarily represent the actual medical status of the disease. This might explain why patients in remission of Cushing's syndrome perceive their illness as chronic or cyclical and believe that psychological attributions might have caused Cushing's syndrome.

The current study also demonstrates that there is a strong relationship between illness perceptions and QoL. This has already been observed in multiple other medical conditions (1). This relationship is a relevant observation, since patients with long-term cure of Cushing's syndrome have persistent complaints reflected in impaired QoL (2-4). These complaints are often misunderstood and difficult to treat.

Therefore, awareness of how these patients perceive their disease and its consequences could lead to a better understanding of Cushing's syndrome and its long-term effects.

In **Chapter 3** we aimed to explore illness perceptions in patients after long-term biochemical control of acromegaly. We used several validated QoL questionnaires and the Illness Perception Questionnaire Revised to assess QoL and illness perceptions. The results indicated that patients with long-term remission of acromegaly have a good understanding of their disease, but they experience a lack of personal control and are not very likely to seek medical care. Interestingly, there are clear differences between illness perceptions in acromegaly and other diseases. For example, acromegalic patients reported more negative illness perceptions than patients with acute pain or vestibular schwannoma, but more positive illness perceptions than patients with chronic conditions, like chronic obstructive pulmonary disease. In addition, patients with long-term remission of acromegaly perceived impaired QoL. The illness perceptions in patients with acromegaly correlated strongly with QoL parameters, in accordance with our observations in patients with long-term cure of Cushing's disease and in other conditions (**Chapter 2**, (1)).

Patients in long-term remission of acromegaly reported somewhat more positive illness perceptions than patients after long-term remission of Cushing's syndrome. It is tempting to speculate that there are disease-specific characteristics in illness perceptions in addition to more general influences related to complaints or chronicity. Additional research is needed to see whether these findings can be extended to other endocrine diseases.

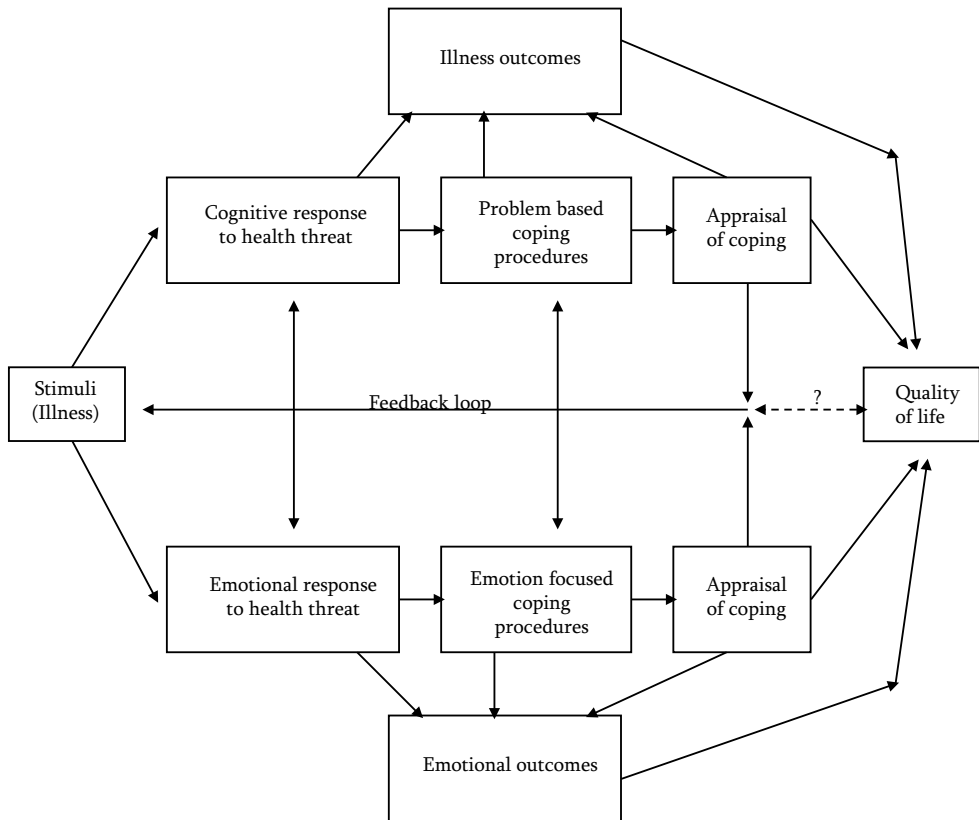
It is important for endocrinologists to explain to the patients what might have caused acromegaly, and ask the patient what their perceived cause of acromegaly is. The illness perceptions of patients, including those pertaining to the perceived cause of acromegaly, are based on various sources which indicates that illness perceptions do not necessarily represent the actual medical status or cause of acromegaly.

The current explorative study is important, since patients with acromegaly suffer from impaired QoL even after long-term remission (5-7). The somatic and psychological factors that contribute to decreased QoL are not well-known, but most likely include musculoskeletal complaints (5), pituitary insufficiency (8;9) and the perception of the patients of their disease.

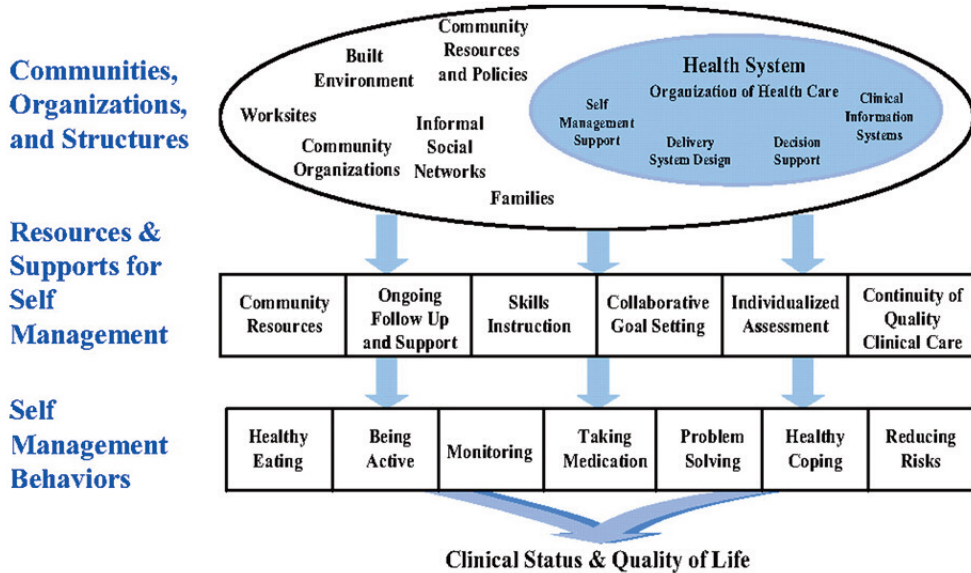
In conclusion, there is a strong correlation between illness perceptions and decreased QoL in patients with long-term remission of Cushing's syndrome as well as in patients after long-term remission of acromegaly. Patients after long-term re-

mission of Cushing’s syndrome reported more negative illness perceptions compared with various reference samples with acute and chronic diseases. Patients with long-term remission of acromegaly reported more negative illness perceptions than patients with acute illness, but more positive illness perceptions than patients with chronic diseases including Cushing’s syndrome.

In the studies described above, the Common Sense Model of self-regulation (CSM) by Leventhal *et al.* was used as starting point to understand the relation between illness, illness perceptions, coping strategies, and outcome (10-13). Based on the performed studies described in this thesis and a recent meta-analytic review of the CSM (14), we postulate that the CSM should incorporate a new arm that represents QoL. The studies described in **Chapter 2** and **Chapter 3** show that illness perceptions and QoL are strongly correlated. We revised the existing CSM, which is depicted in Figure 1. We should note that further research is necessary to establish the correctness of the proposed addition of QoL in the CSM, and whether QoL is involved in the feedback loop of the CSM.



**Figure 1.** The revised Common Sense Model, partially based on Hagger & Orbell (2003)



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**Figure 2.** Trilevel Model of Self-Management and Chronic Care, adapted from Fischer *et al.* (2007)

In addition, the CSM does not encompass contextual factors. These contextual factors are, however, embedded in the Chronic Care Model (CCM) (15). The CCM incorporates self-management into a social context and characteristics of the healthcare system. Both the CSM and the CCM revolve around the central position of the patient in medical care for chronic illnesses. An important difference between the models is that the CCM focuses on beliefs about the target behavior, while the CSM includes beliefs about the illness. Therefore, Fischer *et al.* (16) developed the Trilevel Model of Self-Management and Chronic Care that ties together the CSM and the CCM (see Figure 2).

Based on this Trilevel Model and our findings, we strongly encourage the development of a self-management intervention for (treated) pituitary patients. This intervention should incorporate self-management (17) and should intervene in illness perceptions, which is a dynamic process. Another important aspect to take into account in this intervention is self-efficacy (18;19), which might also play a role in the willingness of patients to change their illness perceptions and/or coping strategies.

We believe that the proposed intervention will ultimately lead to a better QoL, since illness perceptions and QoL are closely related in pituitary diseases. The CSM implies that changing illness perceptions may lead to changes in relevant self-management behaviors. Previous studies have already shown that psycho-



education interventions can indeed change negative illness perceptions (13;20) and thereby self-management and, consequently, outcome (i.e. QoL).

### 3. Coping strategies

In **Chapter 4**, we aimed to investigate coping strategies of patients after treatment for pituitary adenomas. We used the Utrecht Coping Lijst to assess coping. The study demonstrated that patients after appropriate treatment for pituitary adenomas report less active coping, more avoidance coping and seek less social support compared with an a-select sample from the Dutch population. Compared with patients with chronic pain, patients treated for pituitary adenomas sought more social support. Patients after treatment for pituitary disease were also compared with patients in primary care psychology services. Patients with pituitary adenomas scored lower on avoiding, seeking social support, passive coping, and expressing emotions, but higher on active coping. This indicates that patients treated for pituitary adenomas report less effective coping strategies compared with the normal population, but apparently use more effective coping strategies than patients with chronic pain and patients in primary care psychology services. Furthermore, patients after treatment for Cushing's disease, acromegaly, and NFMA did not differ from each other with respect to coping strategies, besides the fact that patients with Cushing's disease sought more social support than patients treated for NFMA.

This is the first study that explored coping strategies in patients treated for Cushing's disease, acromegaly, or NFMA. We believe that information on coping strategies of these patients is important, since they suffer from chronic and multiple disabilities despite long term cure of their initial pituitary adenoma (2-5;21-25), which are often misunderstood and difficult to treat. Knowledge of the coping strategies can be used in designing an intervention based on e.g. cognitive behavioural therapy, self-management training, and information on the negative effects of the disease.

In conclusion, patients treated for Cushing's disease, acromegaly, or NFMA display different and less effective coping strategies compared with healthy controls. Compared with patients with chronic pain and patients receiving primary care psychology services, patients treated for pituitary adenomas report somewhat better coping strategies. Therefore, there is a need to develop, to apply and to evaluate coping skills training and self-management in patients with this condition.

## 4. Cognitive functioning

In **Chapter 5**, we aimed to assess cognitive function in patients after long-term remission of Cushing's disease. We used eleven cognitive tests to assess the entire spectrum of cognition. We compared patients after long-term remission of Cushing's disease with matched controls, and with patients after treatment for NFMA using Z-scores. This study demonstrated that cognitive function is impaired in patients despite long-term cure of Cushing's disease. These patients reported impairments in memory in daily life, which was confirmed by cognitive functioning tests. The performance was decreased in certain aspects of executive functioning and several memory tasks, compared with matched controls. These impairments were not merely related to pituitary disease in general, since these patients with long-term cure of Cushing's disease also revealed impaired cognitive function compared with patients previously treated for NFMA. These observations indicate irreversible effects of previous hypercortisolism on cognitive function and, thus, on the central nervous system.

Several clinical characteristics influenced outcome parameters. Hypopituitarism was associated with mildly impaired executive functioning. Hydrocortisone dependency and additional radiotherapy were negatively associated with memory and executive functioning, whereas the duration of remission positively influenced memory and executive functioning.

Prolonged glucocorticoid excess modifies neurotransmitter function and neuronal structure of the central nervous system (26;27). In rodents, chronic exposure to high levels of glucocorticoids impairs hippocampal long-term potentiation (28), and decreases hippocampal synaptic plasticity (29). In humans, endogenous active Cushing's disease is associated with cognitive impairment (27;30;31). The hippocampus is one of the most sensitive structures in the brain for glucocorticoids and is crucial in cognitive function (32). The persistent impairments in cognitive function in patients with previous Cushing's disease might be explained by irreversible effects of previous glucocorticoid excess on the central nervous system, especially the hippocampus. Additional studies, including functional MRI and postmortem analyses of the central nervous system, are required to evaluate the effects of previous glucocorticoid excess on brain areas of interest.

In **Chapter 8**, we described a cross-sectional study in which we assessed cognitive functioning in patients after long-term remission of acromegaly. We compared these patients with matched controls, and with patients after treatment for NFMA using Z-scores.

We found no differences in cognitive functioning between patients after long-term remission of acromegaly and matched controls or NFMA patients. However,

in contrast, patients with long-term cure of Cushing's disease suffered from impaired cognitive functioning (**Chapter 5**, (3)). We speculate that these differences in cognitive function between patients with long-term cure of acromegaly and patients with long-term cure of Cushing's disease are explained by glucocorticoid-specific, irreversible effects on the central nervous system on structures involved in cognitive function, which are apparently not affected by previous GH/IGF-I excess.

In summary, there are subtle impairments in cognitive function in patients during long-term follow up after cure of Cushing's disease compared with NFMA patients and matched controls. The greatest impairment was present in memory, although executive functioning was also affected. This impairment in cognitive function after treatment of Cushing's disease is not merely the result of pituitary disease in general and/or its treatment, but includes specific elements most likely caused by the irreversible effects of previous glucocorticoid excess on the central nervous system. However, there were no differences in cognitive functioning between patients after long-term remission of acromegaly and matched controls or NFMA patients. We postulate that previous GH/IGF-I excess does not cause irreversible effects on parts of the central nervous system important in cognitive functioning.

## 5. Prevalence of psychopathology

We analyzed the prevalence of psychopathology and maladaptive personality traits in patients after long-term remission of Cushing's disease in **Chapter 6**. We used several validated questionnaires to assess psychopathology, i.e. the Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale, and the Mood and Anxiety Symptoms Questionnaire (short-form). We used the Dimensional Assessment of Personality Pathology (short-form) to evaluate personality traits. This study demonstrated that patients with long-term cure of Cushing's disease suffer from more psychopathology and maladaptive personality traits compared with matched controls. In addition, patients with long-term cure of Cushing's disease had significantly more psychopathology and maladaptive personality traits than patients previously treated for NFMA, indicating that the presence of psychopathology and maladaptive personality traits was not merely related to pituitary tumors and/or their treatment in general. Therefore, the long-term effects of cured Cushing's disease on psychopathology and personality traits are more likely to be the consequence of previous glucocorticoid excess. These observations point to irreversible effects of previous glucocorticoid excess on the central nervous system.

In **Chapter 7**, we reviewed the current literature on psychopathology and Cush-

ing's disease. Active Cushing's disease is associated with a high prevalence of psychopathology, mainly atypical depression. Treatments with glucocorticoid reducing or blocking agents can rapidly relieve symptoms. After successful surgery, prevalence of psychopathology decreases, whereas mood and behavior do not seem to normalize. After long-term remission, patients with Cushing's disease still show decreased QoL and impaired cognitive function.

In **Chapter 8**, we described the prevalence of psychopathology and maladaptive personality traits –as well as cognitive functioning (see section IV. Cognitive functioning)– in patients after long-term remission of acromegaly. We used the same validated questionnaires as the study described in **Chapter 6**, i.e. the Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale, and the Mood and Anxiety Symptoms Questionnaire (short-form). We used the Dimensional Assessment of Personality Pathology (short-form) to evaluate personality traits. The study demonstrated that patients with long-term cure of acromegaly suffer from an increased prevalence of psychopathology and maladaptive personality traits compared with matched controls. Patients with long-term cure of acromegaly also showed more psychopathology, and especially more maladaptive personality traits, compared with patients treated for NFMA. These observations indicate that the increased psychopathology and maladaptive personality traits observed in patients with long-term cure of acromegaly are not merely caused by pituitary adenomas per se and/or their treatment, but rather by previous GH excess. We speculate that the results of our study confirm the clinical impression that patients cured from acromegaly have different and more serious complaints than patients with NFMA, even though patients treated for NFMA have a higher incidence of hypopituitarism.

In summary, patients with long-term cure of Cushing's disease report a high prevalence of psychopathology, compared with both matched controls and patients previously treated for NFMA. Furthermore, patients with long-term cure of Cushing's disease have a greater degree of maladaptive personality traits. In addition, patients with long-term cure of acromegaly also have a high prevalence of psychopathology, compared with matched controls. Patients with long-term cure of acromegaly have a greater degree of maladaptive personality traits, both compared with matched controls and to patients treated for NFMA. The results suggest that these observations reflect irreversible effects of previous glucocorticoid or GH/IGF-I excess on the central nervous system rather than an effect of pituitary tumors and/or their treatment in general. Future studies should aim at further investigating if and how glucocorticoids and GH/IGF-I changes (subclinical) psychopathology.

## 6. Summary and concluding remarks

The present thesis describes the long-term psychological consequences of pituitary diseases. From the studies described in this thesis we can conclude that:

- Patients after long-term remission of Cushing's syndrome have more negative illness perceptions compared with patients with acute and chronic conditions.
- Patients after long-term remission of acromegaly have more negative illness perceptions than patients with acute conditions.
- Illness perceptions and QoL are strongly correlated in patients after long-term remission of Cushing's syndrome, as well as in patients after long-term remission of acromegaly.
- Patients treated for a (non)functioning pituitary adenoma display different and less effective coping strategies compared with healthy controls.
- Patients after long-term remission of Cushing's disease show subtle impairments in cognitive functioning compared with matched controls and NFMA patients.
- There were no differences in cognitive functioning between patients after long-term remission of acromegaly and matched controls or NFMA patients.
- Patients after long-term remission of Cushing's disease or acromegaly have a higher prevalence of psychopathology and maladaptive personality traits than both matched controls and NFMA patients.

Nowadays, pituitary adenomas can be appropriately treated, but patients continue to report impaired QoL despite long-term remission or cure.

In patients with Cushing's disease, Cushing's syndrome or acromegaly, doctors should be aware of subtle cognitive impairments and the increased prevalence of psychopathology and maladaptive personality traits after long-term remission. In addition, these patients use ineffective coping strategies and have negative illness perceptions that are not always correct. Patients are labeled 'cured', but still experience chronic and persisting impairments due to their pituitary disease. Doctors should consider informing patients better about the long-term consequences and act as a guide in this 'acceptance process' of the patient. In addition, a multi-disciplinary team of endocrinologists, psychologists, and community health workers might also help patients in accepting and dealing with the consequences of their pituitary disease.

We strongly encourage the development of a self-management intervention, including coping skills training, for patients with pituitary diseases. This intervention might help these patients to cope with their impairments and change illness perceptions. We postulate that this approach might ultimately lead to a better QoL.

## References

1. **Petrie KJ, Jago LA, Devcich DA.** 2007 The role of illness perceptions in patients with medical conditions. *Curr Opin Psychiatry* 20(2):163-167
2. **van Aken MO, Pereira AM, Biermasz NR, van Thiel SW, Hoftijzer HC, Smit JW, Roelfsema F, Lamberts SW, Romijn JA.** 2005 Quality of life in patients after long-term biochemical cure of Cushing's disease. *J Clin Endocrinol Metab* 90(6):3279-3286
3. **Tiemensma J, Kokshoorn NE, Biermasz NR, Keijser BJ, Wassenaar MJ, Middelkoop HA, Pereira AM, Romijn JA.** 2010 Subtle cognitive impairments in patients with long-term cure of Cushing's disease. *J Clin Endocrinol Metab* 95(6):2699-2714
4. **Tiemensma J, Biermasz NR, Middelkoop H.A.M., van der Mast RC, Romijn JA, Pereira AM.** 2010 Increased prevalence of psychopathology and maladaptive personality traits after long-term cure of Cushing's disease. *J Clin Endocrinol & Metab* 95(10):E129-E141
5. **Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JW, Romijn JA, Roelfsema F.** 2004 Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. *J Clin Endocrinol Metab* 89(11):5369-5376
6. **Bonapart IE, van Domburg R, ten Have SM, de Herder WW, Erdman RA, Janssen JA, van der Lely AJ.** 2005 The 'bio-assay' quality of life might be a better marker of disease activity in acromegalic patients than serum total IGF-I concentrations. *Eur J Endocrinol* 152(2):217-224
7. **Rowles SV, Prieto L, Badia X, Shalet SM, Webb SM, Trainer PJ.** 2005 Quality of life (QOL) in patients with acromegaly is severely impaired: use of a novel measure of QOL: acromegaly quality of life questionnaire. *J Clin Endocrinol Metab* 90(6):3337-3341
8. **Paisley AN, Rowles SV, Roberts ME, Webb SM, Badia X, Prieto L, Shalet SM, Trainer PJ.** 2007 Treatment of acromegaly improves quality of life, measured by AcroQol. *Clin Endocrinol (Oxf)* 67(3):358-362
9. **Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X, Webb SM, van der Lely AJ.** 2008 Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant. *J Clin Endocrinol Metab* 93(10):3853-3859
10. **Leventhal H, Diefenbach M, Leventhal EA.** 1992 Illness cognition: Using common sense to understand treatment adherence and affect cognition interactions. *Cognit Ther Res* 16(2):143-163
11. **Leventhal H, Meyer D, Nerenz D.** The common sense representation of illness danger. In: Rachman S, editor. *Contributions to medical psychology*. New York: Pergamon Press, 1980: 7-30.
12. **Leventhal H, Brissette I, Leventhal EA.** The common-sense model of self-regulation of health and illness. In: Cameron LD, Leventhal H, editors. *The self-regulation of health and illness behaviour*. London: Routledge, 2003: 42-65.
13. **McAndrew LM, Musumeci-Szabo TJ, Mora PA, Vileikyte L, Burns E, Halm EA, Leventhal EA, Leventhal H.** 2008 Using the common sense model to design interventions for the prevention and management of chronic illness threats: from description to process. *Br J Health Psychol* 13(Pt 2):195-204
14. **Hagger MS, Orbell S.** 2003 A meta-analytic review of the common-sense model of illness representations. *Psychol Health* 18(2):141-184
15. **Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A.** 2001 Improving chronic illness care: translating evidence into action. *Health Aff (Millwood)* 20(6):64-78
16. **Fisher EB, Brownson CA, O'Toole ML, Anwuri VV, Shetty G.** 2007 Perspectives on self-management from the Diabetes Initiative of the Robert Wood Johnson Foundation. *Diabetes Educ* 33 Suppl 6:216S-224S
17. **Jansen DL, Heijmans M, Rijken M, Kaptein AA.** 2011 The Development of and First Experiences with a Behavioural Self-regulation Intervention for End-stage Renal Disease Patients and Their Partners. *J Health Psychol* 16(2):274-283
18. **Lau-Walker M.** 2006 Predicting self-efficacy using illness perception components: a patient

- survey. *Br J Health Psychol* 11(Pt 4):643-661
19. **Lau-Walker M.** 2007 Importance of illness beliefs and self-efficacy for patients with coronary heart disease. *J Adv Nurs* 60(2):187-198
  20. **Petrie KJ, Cameron LD, Ellis CJ, Buick D, Weinman J.** 2002 Changing illness perceptions after myocardial infarction: an early intervention randomized controlled trial. *Psychosom Med* 64(4):580-586
  21. **Biermasz NR, van Dulken H, Roelfsema F.** 2000 Long-term follow-up results of postoperative radiotherapy in 36 patients with acromegaly. *J Clin Endocrinol Metab* 85(7):2476-2482
  22. **Biermasz NR, van Dulken H, Roelfsema F.** 2000 Ten-year follow-up results of transsphenoidal microsurgery in acromegaly. *J Clin Endocrinol Metab* 85(12):4596-4602
  23. **Biermasz NR, Pereira AM, Smit JW, Romijn JA, Roelfsema F.** 2005 Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life. *J Clin Endocrinol Metab* 90(5):2731-2739
  24. **Tiemensma J, Biermasz NR, vd Mast RC, Wassenaar M.J.E., Middelkoop H.A.M., Pereira AM, Romijn JA.** 2010 Increased psychopathology and maladaptive personality traits, but normal cognitive functioning, in patients after long-term cure of acromegaly. *J Clin Endocrinol Metab* 95(12):E392-402
  25. **Dekkers OM, van der Klaauw AA, Pereira AM, Biermasz NR, Honkoop PJ, Roelfsema F, Smit JW, Romijn JA.** 2006 Quality of life is decreased after treatment for nonfunctioning pituitary macroadenoma. *J Clin Endocrinol Metab* 91(9):3364-3369
  26. **Starkman MN, Gebarski SS, Berent S, Schteingart DE.** 1992 Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. *Biol Psychiatry* 32(9):756-765
  27. **Forget H, Lacroix A, Somma M, Cohen H.** 2000 Cognitive decline in patients with Cushing's syndrome. *J Int Neuropsychol Soc* 6(1):20-29
  28. **Foy MR, Stanton ME, Levine S, Thompson RF.** 1987 Behavioral stress impairs long-term potentiation in rodent hippocampus. *Behav Neural Biol* 48(1):138-149
  29. **Bodnoff SR, Humphreys AG, Lehman JC, Diamond DM, Rose GM, Meaney MJ.** 1995 Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity, and hippocampal neuropathology in young and mid-aged rats. *J Neurosci* 15(1 Pt 1):61-69
  30. **Hook JN, Giordani B, Schteingart DE, Guire K, Giles J, Ryan K, Gebarski SS, Langenecker SA, Starkman MN.** 2007 Patterns of cognitive change over time and relationship to age following successful treatment of Cushing's disease. *J Int Neuropsychol Soc* 13(1):21-29
  31. **Mauri M, Sinforiani E, Bono G, Vignati F, Berselli ME, Attanasio R, Nappi G.** 1993 Memory impairment in Cushing's disease. *Acta Neurol Scand* 87(1):52-55
  32. **McEwen BS.** 2008 Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *Eur J Pharmacol* 583(2-3):174-185

