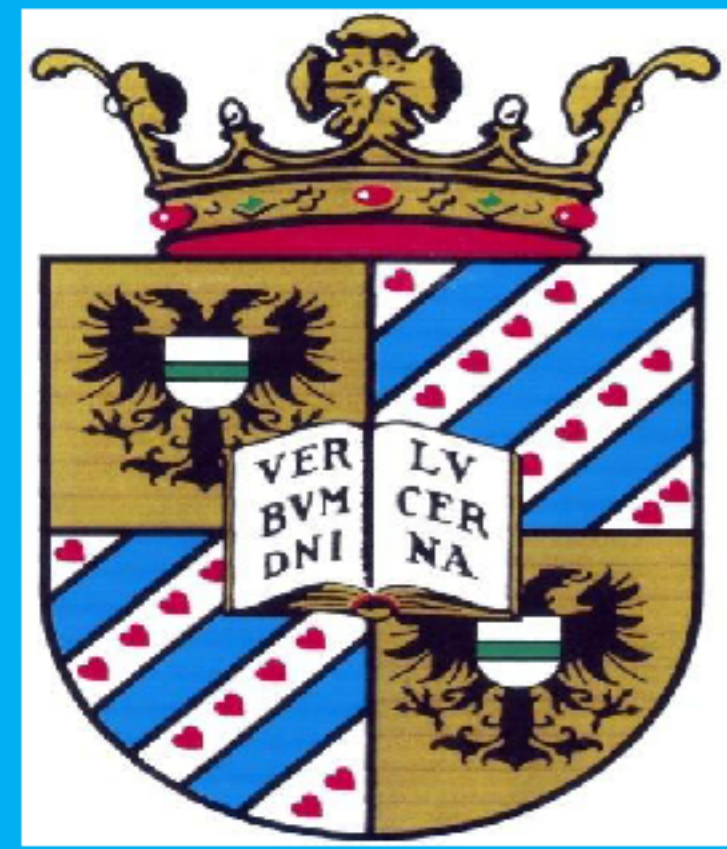


# Hydrocortisone dose influences pain perception, depressive symptoms, and perceived health in patients with secondary adrenal insufficiency – a Randomized Controlled Trial.



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## Background

There is a major lack of randomized controlled trials evaluating the effects of hydrocortisone (HC) substitution therapy on health-related quality of life (HR-QoL) in patients with adrenal insufficiency (AI). Evidence for clinical guidelines with respect to the HC dose is mostly based on cross-sectional studies and expert opinion.

## Objective

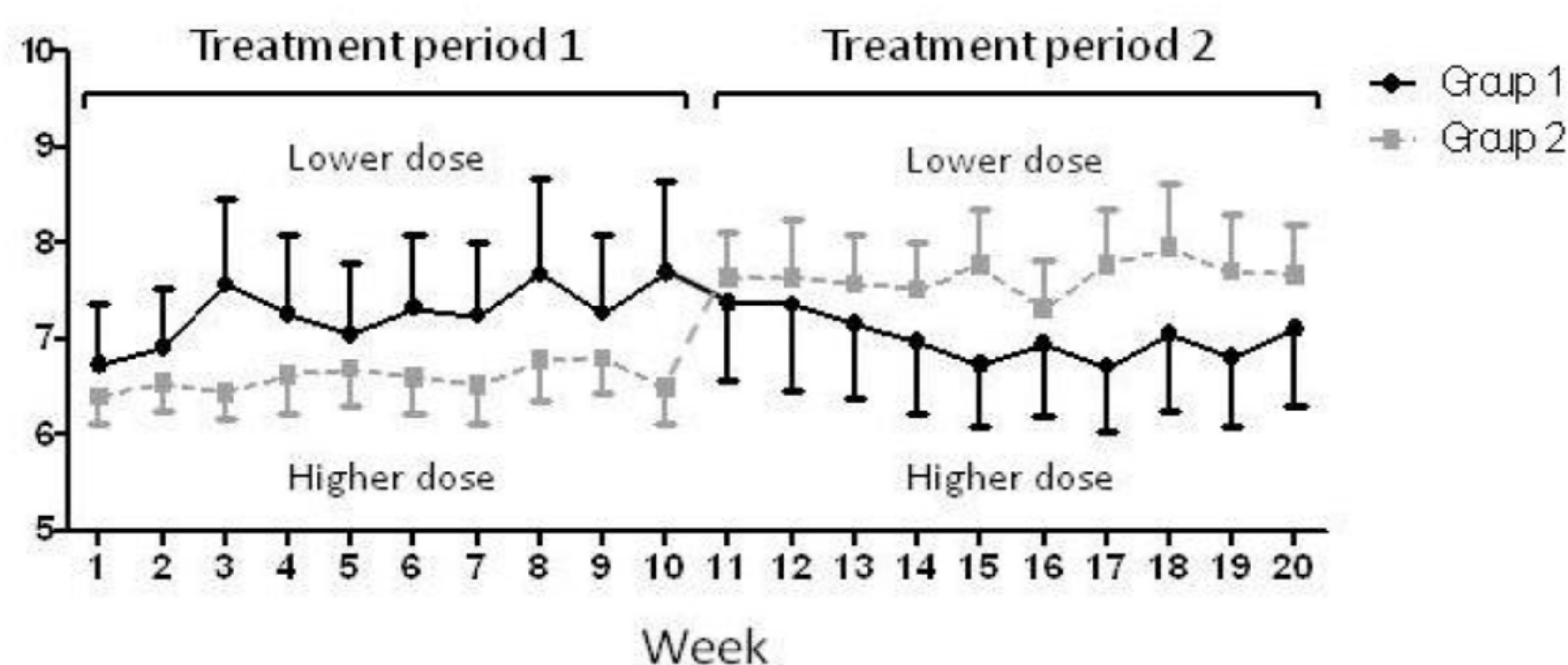
To determine the effect of the total daily dose of HC on HR-QoL by comparing a lower physiological dose of HC to a higher physiological dose of HC in patients treated for secondary AI in a randomized, double-blind, crossover study.

## Methods

Forty-seven patient with secondary AI participated (29 men, age  $51 \pm 14$  (range 19-73) years). Patients randomly received first a low dose HC (0.2-0.3 mg/kg body weight) for 10 weeks, followed by a higher dose HC (0.4-0.6 mg/kg body weight) for another 10 weeks, or vice versa. HC substitution was given in three divided doses with the highest dose in the morning.

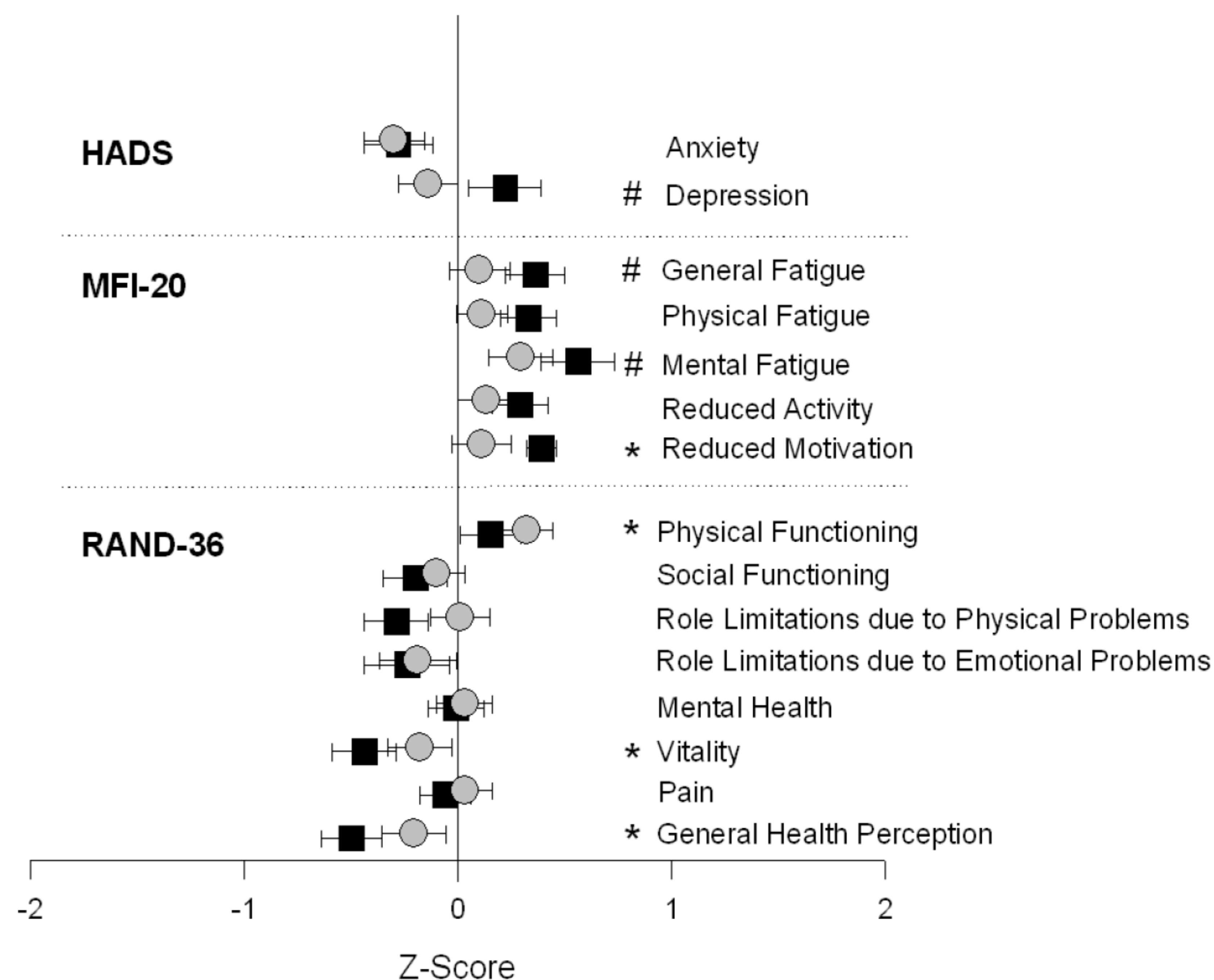
At the end of each treatment period, patients were asked to complete the Hospital Anxiety and Depression Scale (HADS), the Multidimensional Fatigue Inventory-20 (MFI-20), the RAND-36 item Health Survey (RAND-36), and the Cognitive Failures Questionnaire (CFQ). Furthermore, patients were instructed to complete a daily mood and symptoms diary, consisting of the Patient Health Questionnaire-15 (PHQ-15), the Generalized Anxiety Disorder-7 (GAD-7), and the Patient Health Questionnaire-9 (PHQ-9).

Differences in HR-QoL measures between the lower and the higher dose were assessed with the Wilcoxon Signed Rank Test for paired data. The two-sided significance level was set at  $P < 0.05$ .



**Figure 2. Pain scores plotted for each week.**

For the composite pain score, the items 'stomach pain', 'back pain', 'pain in arms, legs or joints', 'headache' and 'chest pain' of the Patient Health Questionnaire-15 were summed up, with scores ranging from 5 to 35. Scores represent mean  $\pm$  SEM.



**Figure 1. Z-scores for HADS, MFI-20 and RAND-36 for patients treated for secondary adrenal insufficiency.**

Higher HADS scores indicate more anxiety and/or depression, higher MFI-20 scores indicate more fatigue, higher RAND-36 scores indicate better quality of life. Grey circles represent scores on the higher dose, black squares represent scores on the lower dose. Data represent mean  $\pm$  SEM.

\*  $P < 0.05$ .

# A significant period effect was found in addition to a significant treatment effect

## Results

While receiving the higher dose of HC, patients reported significantly fewer depressive symptoms ( $P = 0.016$  and  $P = 0.045$  for HADS and PHQ-9, respectively), less general and mental fatigue ( $P = 0.004$  and  $P = 0.003$ , respectively), increased motivation ( $P = 0.021$ ) (MFI-20), better physical functioning ( $P = 0.041$ ), better general health ( $P = 0.013$ ) and more vitality ( $P = 0.025$ ) (RAND-36) as compared to while receiving the lower dose (Fig 1). In addition, while on the higher dose fewer somatic symptoms ( $P = 0.022$ ), particularly less pain ( $P < 0.001$ ) (PHQ-15), were experienced (Fig 2). No differences were found between the doses for anxiety (HADS and GAD-7) and self-reported cognitive failures (CFQ).

## Conclusion and relevance

While on the higher dose of HC, patients reported a better HR-QoL with regard to general health, mental health, depressive symptoms, common somatic complaints, pain and fatigue as compared to the lower dose of HC. Effects on HR-QoL are important in individualizing the HC substitution dose.

