**Aus der Klinik für Endokrinologie, Diabetologie und Rheumatologie**

**Medizinische Fakultät**

**Direktor: Univ.Prof. Dr. med.Werner A. Scherbaum**

# SCHLAFSTÖRUNGEN BEI LUPUS ERYTHEMATODES PATIENTEN

## Teil der LuLa Studie

**Dissertation**

**Zur Erlangung des Grades eines Doktors der Medizin/Zahnmedizin**

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**Mariam Asfour**

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# SLEEPING DISORDERS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

## Part of the LuLa STUDY

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gez: Univ.-Prof. Dr.med. Joachim Windolf

1. Gutachter: Prof. Dr. med. Matthias Schneider, Rheumatologie, HHU

2. Gutachter: Dr. med. Christof Specker, Klinikum Essen Süd

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# 1 Introduction

Systemic Lupus Erythematosus (SLE) is a rare autoimmune disease accompanied by multiple organ impairment and increased mortality (Cook et al. 2000). More than half of the patients with SLE develop a characteristic red, flat facial rash over the bridge of their nose. Because of its shape, it is frequently referred to as the "butterfly rash" of SLE. The rash is painless and does not itch. The facial rash, along with inflammation in other organs, can be precipitated or worsened by exposure to sunlight, a condition called photosensitivity. This photosensitivity can be accompanied by worsening of inflammation throughout the body, called a "flare" of disease.

The disease is known to affect kidney, joints, heart, lung and brain. It may cause hypertension, chronic renal disorders, diabetes, cancer, chronic lung disease as well as chronic liver and gastric disease, high cholesterol, cardiovascular disease, skin scarring, osteoporosis, fibromyalgia, thromboembolic disease and depression (NIAMS 2009).

The diagnosis of the disease is sometimes difficult. The specialized rheumatologists need blood tests for complement level and ANA as well as other antibodies such as anti-DNA, anti-Sm, anti-RNP, anti-Ro (SSA), and anti-La (SSB). They may ask for skin or kidney biopsies and may take radiographs to determine the involvement of certain organs (NIAMS 2009) to be able to diagnose the disease.

SLE is also characterized by many disorders such as sleep disturbance, fatigue, reduced muscle strength and physical disability that are somehow related to the disease activity and severity (Tench et al. 2000; Brey and Petri 2003; Lashley 2003). The consequences of chronic poor sleep may be depression to fatigue (Lash 1998; Sweet et al. 2004) and a poorer quality of life (Brey and Petri 2003).

It is difficult to measure sleep and fatigue due to the subjective influence and the way the patients evaluate the quantity and quality of sleep they get. Attempts have been made to measure this in sleep laboratories. However, the VSH Sleep Scale (Corzillius et al. 1991) was found best to measure sleep by the patients themselves by means of a list of specific questions and scales in order to evaluate the answers into useful information.

The sleep scores used to measure sleep are grouped under a VSH sleep scale. This score measures sleep disturbance, sleep effectiveness and sleep supplementation.

## 2 Aim and objective of the study

This study is aimed at assessing the sleep disturbance in a fairly large number of patients with Systemic Lupus Erythematosus. The patients are members of a self-help-organization in Germany called Deutsche Lupus Erythematodes Selbsthilfegemeinschaft e.V. (SHG).

The Lula Study is a project running for a period of ten years. Once a year a questionnaire is prepared by the department of Rheumatology at the University of Düsseldorf and is sent to the patients in order to self-assess the disease from the patient's point of view. The patients answer on a scale that can be used to evaluate statistically the outcome and to get significant results.

The self assessment questionnaire in 2005 was sent to almost 1000 patients. In that year, it was developed to assess, among other issues, their sleep and fatigue over the last 6 months period. Sleep quality and quantity as well as duration and time needed to fall asleep are investigated in relation to other variables as the age of the patient, pain, severity and duration of the disease and presence of accompanying diseases as well as the use of medication. The evaluation is carried out with the Pittsburgh sleep quality index (PSQI).

**The questions to be answered by this study are:**

- **Are sleep disorders common in patients with Systemic Lupus Erythematosus?**
- **Is there any correlation between Systemic Lupus Erythematosus expression and sleep disturbance?**
- **Which factors influence the sleep quality in patients with Systemic Lupus Erythematosus (age, certain medication, accompanying diseases)?**
- **Is there a correlation between sleep and perceived pain?**

This and further studies can offer information to newly diagnosed patients and may lead to provide a better treatment or symptomatic relief for patients with Systemic Lupus Erythematosus.

# 3 Systemic Lupus Erythematosus

Systemic Lupus Erythematosus is a rare (Jimenez et al. 2003) autoimmune disease generally affecting many organs and having a high mortality rate (Cook et al. 2000).

SLE is spread worldwide with an incidence of 0.4-9.2 newly affected patients/100.000 persons/year. The prevalence varies in Europe 25-27/100.000, in Asia 49/100.000 and in Africa more than 200/100.000. This disease affects more female patients than males with a ratio of 9:1. SLE affects women mostly in the 3rd or 4th decade of life (NIAMS 2009).

The 10 year survival rate ranges nowadays between 85-90% (Urowitz and Gladman 1999). Since the first description of the disorder by Kaposi in 1872, neuropsychiatric abnormalities as well as sleep disturbance and fatigue have been associated strongly with SLE (McCune and Golbus 1988; Ainiala et al. 2001). CNS involvement can be focal, multi-focal or in form of diffuse brain disturbance (Sweet et al. 2004).

## 3.1 Pathophysiology of the disease

Systemic Lupus Erythematosus is characterized by a hyperactivity of the immune system in form of an overproduction of auto antibodies of the T-cell dependant B-cell stimulation. The autoimmune reaction may affect any organ where auto-antibodies are deposited but most frequently the joints, the mucosa as well as the skin and in severe cases kidneys and CNS are involved.

Despite the fact that genetics play an important role, there exists no specific SLE gene which predisposes people to get ill with SLE (NIAMS 2009).

### 3.2 Clinical manifestations

The disease manifests itself by skin rashes, joint pain and renal involvement as well as CNS involvement. The skin is very sensitive to sunlight. In many situations a characteristic butterfly reddish rash is visible on the face. Joint pain comes in bursts.

The neuropsychiatric syndromes impacting the CNS observed in SLE are cerebrovascular disease, seizure disorders, psychosis, acute confusional state, aseptic meningitis demyelinating syndrome, movement disorder, myelopathy, cognitive dysfunction, anxiety, mood disorder and headache (Sweet et al. 2004).

Despite fluctuations in the disease activity, patients with SLE cope with the disease as the time passes. However about 40% remain distressed (Dobkin et al. 2001); this is mainly due to fatigue caused by sleep disruption and depression (McKinley et al. 1995). Pain and depression found to be positive predictors of fatigue (Jump et al. 2005).

### 3.3 Disease Activity

Clearly, the disease manifests itself by a variety of symptoms which are not identical for all patients.

Most recent studies rely on patients self assessments and questionnaires. Adams et al. in 1994 followed 41 patients who self-monitored physical and psychological symptoms over a 49 day period and found that stress, depression and anger predicted joint pain, rash and abdominal distress as well as temperature elevations (Adams et al. 1994).

Jump et al. found that pain and depression were both unique positive predictors of fatigue. Controlling for pain and depression, perceived social support contributed negatively to the variance in fatigue scores, suggesting a buffering effect. In contrast, disease activity measured by SLEDAI does not appear to account for fatigue in SLE. Understanding the effect of psychosocial factors on fatigue in SLE may improve patient outcomes through psychosocial interventions aimed at reducing pain and increasing coping skills and social support (Jump et al. 2005).

Some scoring systems that have been developed to classify the disease activity are as follows:

SLAM

The Systemic Lupus Activity Measure (SLAM) consists of 25 clinical criteria and 7 laboratory criteria. Each of the findings is rated as 1 = no involvement , 2 = light involvement and 3 = severe involvement. All the points are collected, and they may vary from 0 to 85. The higher the score, the more active is the disease ((Liang et al. 1989; Bae et al. 2001).

ECLAM

The European Consensus Lupus Activity Measurement Index (ECLAM) can be used to evaluate disease activity in patients retrospectively from the data provided in their clinical charts (Mosca et al. 2000).

BILAG

The BILAG (British Isles Lupus Assessment Group) is a comprehensive computerised index for measuring clinical disease activity in SLE. It was developed according to the principle of the 'physicians' intention to treat'. The index allocates separate alphabetic scores to each of eight organ-based systems. It demonstrated a good 'between-rater' reliability for each organ based system. Based on the answers to the questionnaire the BLIPS software will calculate a clinical score. This scoring system has been derived by considering what features of SLE usually prompt a physician to increase disease-specific therapy (steroids or immuno-suppressants) (Hay et al. 1993; Isenberg and Gordon 2000).

SLEDAI

The Systemic Lupus Erythematosus Disease Activity (SLEDAI) is a "weighted" index of 9 organ systems for disease activity in SLE and the questions are grouped as follows: 8 for central nervous system and vascular, 4 for renal and musculoskeletal, 2 for serosal, dermal, immunologic, and 1 for constitutional and hematologic. The maximum theoretical score is 105, but in practice few patients have scores greater than 45. The SLEDAI predicted well the physicians' ratings in the testing set. Therefore SLEDAI is a validated model of experienced clinicians' global assessments of disease activity in lupus. It represents the consensus of a group of experts in the field of lupus research (Bombardier et al. 1992).

SLAQ

The Systemic Lupus Activity Questionnaire (SLAQ) is a scoring system validated for population studies. Its positive predictive values ranged from 56-89% for detecting clinically significant disease activity (Karlson et al. 2003). Because it is primariliy revealing the patients' perception of the disease it was used for the present study.

### 3.4 Treatment of the disease

The disease is treated by a variety of drugs as the following summary shows:

A **Analgetics** are prescribed according to the WHO pain medication "ladder", WHO 1986). In the first step non steroidal antirheumatic drugs (NSAR) such as Paracetamol, Ibuprofen, Acetyl Salicilic Acid, Metamizol and Diclofenac are given. Some have anti inflammatory effects. Because some of the NSAR have adverse effects on the stomach and kidneys (esp. in case of renal involvement), it is not always possible to give higher doses of these drugs and the second step of the WHO must be applied: The NSAR are replaced by a medium potency opioid, e.g. Codein, Tramadol (Tramal, Tilidin/Naloxon) and they can be freely

prescribed by German physicians. In case of ineffectivity Morphin will be the drug of choice. In the third step drugs of the 1st step plus opioids may be the assistance of anti vomiting therapy/anti nausea therapy.

B **Antimalarial drugs** such as Resochin/Quensyl) (Parke 1988; Meinao et al. 1996; Borba and Bonfa 2001)

C **Corticosteroids** are used in severe SLE to suppress the inflammatory process and help to relieve the complications and symptoms, including anemia and kidney involvement. Prednisolone is used to slow down the disease process. Oral prednisone is usually prescribed. Other agents include Solumedrol, hydrocortisone, and Medrol/Decadron (Balow 1990; Kahn 1990; Venables 1993; Roberts 1997).

A corticosteroid therapy must be individually adjusted and the regimen varies widely depending on the severity and location of the disease: Some people need to take oral prednisone for a short time only. Others may require it for a long duration. An intravenous administration of methylprednisolone using "pulse" therapy for three days has proven useful. Combinations with other drugs, particularly immunosuppressants, may be beneficial.

Side effects of long-term oral corticosteroids include cataracts, glaucoma, osteoporosis, diabetes, fluid retention, susceptibility to infections, weight gain, hypertension, capillary fragility, acne, excess hair growth, wasting of the muscles, menstrual irregularities, irritability, insomnia, and psychosis. Medications that can prevent osteoporosis include calcium supplements, parathyroid hormone, alendronate etidronate, risedronate, or hormone replacement therapy in postmenopausal women.

D **Immunosuppressants** are used for about one third of patients, either alone or with corticosteroids for very active SLE, particularly when kidney or neurologic involvement or acute blood vessel inflammation is present. Specific immunosuppressants are:

- Azathioprine (Miescher and Beris 1984; Abu-Shakra and Shoenfeld 2001; Houssiau and Ginzler 2008)
- Methotrexate (Fox and McCune 1994; Sato 2001)
- Cyclophosphamide tablets or infusion. Pulsed administration of cyclophosphamide is effective in improving long-term outcome in patients with kidney involvement. A combination with a pulsed corticosteroid may prove to be even better without posing a risk of additional side effects. High-dose cyclophosphamide can achieve remission in certain patients with severe SLE who are not improving with prednisone or other agents. Regimens using oral or low-dose IV cyclophosphamide in combination with other agents, notably azathioprine, are also reporting good results. Until recently, many physicians considered cyclophosphamide the gold standard of treatment (Ahmed and Hombal 1984; McCune and Fox 1989; De Vita et al. 1991; Bargman 2009)
- Mycophenolatmofetil (MMF) shows particular effectiveness for renal complications. It was shown that in patients with severe lupus nephritis MMF is as effective as daily cyclophosphamide and superior to monthly cyclophosphamide therapy. Patients may receive MMF as an initial treatment, or it may be given once remission has been achieved by another drug first. One particularly effective approach entails initial treatment with cyclophosphamide followed by maintenance with MMF (Adu et al. 2001; Ginzler and Aranow 2005; Moore and Derry 2006; Zhu et al. 2007; Jones et al. 2009).

General side effects of immunosuppressants are frequently stomach and intestinal distress, skin rash, and mouth sores. Hair loss can occur. Over-suppression of the immune system can cause low blood cell counts and serious side effects, including anaemia, menstrual irregularity, possible ovarian failure and permanent infertility, herpes zoster (shingles), liver and bladder toxicity, and an increased risk of cancer.

### 3.5 Prognosis of the disease

This chronic disease affects many organs and occurs in bursts with morbidity and mortality influenced by many factors such as socioeconomic status, habits, medical treatment and patients compliance as well as life stress. Regarding survival as outcome variable, the prognosis for patients with SLE has changed from high early mortality to a more chronic long term course during the past decades (Zink et al. 2004; Fischer-Betz et al. 2005). The 5 year survival rates are 95% while the 20 year survival rate varies from 53-68%. The causes of death are mainly infectious due to low immunity and high cardiac and cerebro-vascular complications.

Another prognostic aspect is the patient's long-term quality of life. Systemic lupus as characterized by episodes of exacerbation and remission results in varying levels of health status. Measuring quality of life by means of the SF-36 showed that minimally clinical improvements which were perceived by the patients were reflected by increasing points on the SF-36 scales (Strand et al. 2003). Other studies pointed out that the long course of the disease leads to coping and that therefore the quality of life remains stable (Fortin et al. 1998; Gilboe et al. 2001; Panopalis et al. 2005). In spite of these findings, the cited authors stated that it is important to survey the patient's well-being regularly because changes concerning the quality of life are expected if the course of the disease is changing.

# 4 Sleep and sleep disturbance in SLE patients

## 4.1 Sleep disturbance

Sleep is essential for health and quality of life (Asplund 1999). Insomnia is a subjective complaint of dissatisfaction with the quantity, quality or timing of sleep (Brey and Petri 2003) and a prior insomnia is a major predictor for major depression (Breslau et al. 1996). This disorder is estimated to occur in approximately 12% to 25% of the general population, although this is probably an underestimate as there is evidence that many adults do not report their sleep problems to a health care professional (Buysse et al. 1989; Dobkin et al. 2001).

## 4.2 Sleep and SLE

Sleep disturbance and fatigue are described generally as particular symptoms affecting the quality of life of patients with SLE (Sweet et al. 2004).

Many patients with SLE relate their poor sleep to pain and vegetative symptoms as breathlessness, sweating and palpitations (Gudbjornsson and Hetta 2001). The periodic limb movement during sleep is a characteristic feature in some SLE patients. Valencia-Flores also showed abnormality in sleep architecture: Patients with SLE have frequent alpha wave intrusions in the sleep EEG. However, this may have been an overestimate due to small sample size (n=14) (Valencia-Flores et al. 1999) This pattern of EEG has been associated with complaints of non-refreshing sleep and fatigue (Moldofsky et al. 1975).

Fatigue in Systemic Lupus Erythematosus is related to contributions of disease activity, pain, depression, and social support and prior insomnia is a major predictor for major depression (Breslau et al 1996).

## 4.3 Measurement of sleep disturbance

Although sleep quality is a readily accepted clinical construct, it represents a complex phenomenon that is difficult to define and measure objectively. Sleep quality can mean sleep duration, sleep latency, number of arousals and depth and restfulness of sleep. Many of these quality items are subjective and should be measured or interpreted by the patient himself. This led to the need to develop a sleep quality index to provide reliable standardized information for comparison between groups and individuals (Buysse et al. 1989).

**Sleep scores for the measurement of sleep quality**

VSH Sleep Scale

The Verran and Snyder-Halpern Sleep Scale (VSH Sleep scale) utilizes three scales (sleep disturbance, sleep effectiveness, and sleep supplementation) to characterize overall sleep quality (Snyder-Halpern and Verran 1987). Psychometric testing of this sleep scale has been conducted in ambulatory and hospitalized patient populations. Sleep quality (as measured by the sleep disturbance scale) was considered the primary outcome parameter in the present study.

The sleep disturbance scale characterizes sleep fragmentation and latency as measured by seven sleep properties. Fragmentation characteristics include mid-sleep awakening, wake after sleep onset, movements during sleep, soundness of sleep, and quality of disturbance while latency characteristics include sleep latency and quality of latency. Each characteristic is measured using a 100 mm visual analogue scale and the total score for the primary outcome of sleep disturbance is a sum of the scores from each scale (total score maximum 700). A lower total score on this scale indicates a lower degree of sleep disturbance.

The secondary outcome parameters for this study included the degree of sleep effectiveness and sleep supplementation (and their determinants) as measured by the VSH Sleep Scale.

The sleep effectiveness scale measures both quality and length of sleep as perceived by the patient using the following five characteristics: rest upon awakening, subjective quality of sleep, sleep sufficiency evaluation, total sleep time, and total sleep period. A visual analogue scale is used to measure each of the five items and these scores are summed to represent a total score. The maximum possible total score is 500 with a higher score representing greater sleep effectiveness.

The sleep supplementation scale measures the degree to which the bulk sleep period is augmented with additional sleep time. The four characteristics measured are daytime sleep, morning sleep, afternoon sleep, and wake after final arousal. The scores from each of these scales are summed to obtain a total score (total score maximum 400). In addition, the total sleep period is calculated by adding the scores from wake after sleep onset and total sleep time. A higher total score on this scale represents a worse outcome, as more supplemental sleep was needed.

The VSH Sleep Scale was validated in several studies (Snyder-Halpern and Verran 1987; Redeker et al. 1998; Tranmer et al. 2003).

**Pittsburgh Sleep Quality Index (PSQI)**

The Pittsburgh Sleep Quality Index (PSQI) is an effective and valid instrument for measuring retrospectively quality and quantity of sleep over a 1-month period using self-reports. It differentiates “poor” from “good” sleep by sampling 18 items allocated to 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. Scoring of answers is based on a 0-3 scale. A global sum of the component scores is calculated with a possible total value ranging from 0-21.

A higher score corresponds to decreased quality of sleep. An empirically defined cut-off-value of 5 allows a graduation in “good” and “poor” sleepers. A score >5 indicates “poor” sleep, whereby a value >10 depicts severe chronic sleep disturbances (Buysse et al. 1989; Buysse et al. 1991).

The PSQI has been validated in several studies (Backhaus et al. 2002; Beck et al. 2004; Cole et al. 2006).

# 5 Material and Methods

## 5.1 Patient recruitment

The patients included in this study were members of the German self-help group "Deutsche Lupus Erythematodes Selbsthilfegemeinschaft" (SHG), which was established in 1986. Membership in the SHG was the only inclusion criterion.

All members of the SHG receive automatically the "Schmetterling", a periodical that is published every quarter and informs the members about all what is new in the disease, treatment, meetings of the different groups in the different cities in Germany, seminars, etc.. There is no added privilege for people included in this study.

The assessment is part of the LuLa study that started in 2001 and continues for a total duration of 10 years. The patients are selected when they fill the questionnaire and send it back to the Headquarters of the SHG. The questionnaire treats the health situation as a whole. The questionnaires are used to be sent to the patients with the "Schmetterling" issue at the beginning of each year. The questionnaires that are included in the study are those that are complete and correctly filled by the patients within the time limit set.

The questionnaire of 2005 is filled out by the members of the SLE-self help community in a way that ensures the data protection system: the questionnaire has at its top a space for a numeric code that the patient fills out instead of his name. The numeric codes are the membership codes of the SHG and are not known by the evaluators. A stamped envelope is provided with the questionnaire to allow the uncomplicated anonymous return of the filled questionnaires. (The names that correspond to the various membership numbers are kept confidential at the headquarters of the self help group). The members answer the questionnaire. The answered envelopes are posted to the dept of Rheumatology at the University of Düsseldorf.

This study involves the sequence of the disease, its therapy as well as the quality of life of the patients and the demographic factors. This questionnaire is updated on yearly basis by the Staff members of the Department of Rheumatology and is used for the

cross-sectional and longitudinal analysis of the disease. Each year several constant points are included in the questionnaire. These are: the general health situation, co-morbidities and the medications used in the treatment. Each year a new theme is analyzed and the questionnaire of 2005 was focusing on sleep.

## 5.2 The questionnaire

See Appendix 1 (Scan Questionnaire/ Fragebogen 2005)

A questionnaire was developed integrating the Pittsburgh Quality and Quantity Indices (Buysse et al. 1989; Buysse et al. 1991). The indices were analyzed and validated for population studies and a new questionnaire was developed to self evaluate the disease activity: SLAQ = Systemic Lupus Activity Questionnaire based on SLAM = Systemic Lupus Activity Measure (Karlson et al. 2003). In a study in Kiel (Germany), SLAM was compared with two other indices to evaluate the disease activity and was found in particular, to be suitable for retrospective evaluation of the disease activity in SLE (Corzillius et al. 1991). The validation of this index is used here in a new questionnaire to SLE patients in Germany in the form of a separate study.

The LuLa Study received the approval of the ethical committee of the Heinrich-Heine-University under the No 2260.

## 5.3 PSQI

The Pittsburgh Sleep Quality Index (PSQI) is an effective and valid instrument for measuring retrospectively quality and quantity of sleep over a 1-month period using self-reports. In Germany the PSQI was validated in 2002 by Backhaus et al.. They evaluated 80 patients with a primary insomnia and 45 healthy controls and found that a cut-off-value of 5 reliably separates “good sleepers” from “poor sleepers (sensitivity 98.7; spe-

cificity 84.4). The mean PSQI of "poor sleepers" (13.39) significantly exceeded the cut-off-value (Backhaus et al. 2002).

A higher score corresponds to decreased quality of sleep. An empirically defined cut-off-value of "5" allows a graduation in "good" and "poor" sleepers. A score >5 indicates "poor" sleep, whereby a value >10 depicts severe chronic sleep disturbances (Buysse et al. 1989; Buysse et al. 1991).

The PSQI contains 19 self-evaluating questions and 5 questions to be answered by the partner or flat mate if available. In this evaluation only the answers to the self evaluating questions are taken into consideration. These questions are divided in 7 components. Each component can obtain a value between 0 and 3 points then the 7 components are added together to give a total value between 0-21.

The point value calculation is as follows:

**First Component : Subjective sleep quality**

The quality of sleep was evaluated in a score from 0 for very good sleepers to 3 in very poor sleepers

Evaluate question No 6 as follows:

| **Answer** | | **Point Value** | | |
|---|---|---|---|---|
| Very good (sehr gut) | = | 0 | | |
| Fairly good (ziemlich gut) | = | 1 | | |
| Fairly bad (ziemlich schlecht) | = | 2 | | |
| Very bad (sehr schlecht) | = | 3 | | |
| | | | **Component 1:** | **…….** |

**Second Component: Latency of sleep (minutes)**

Evaluate question 2 as follows:

| **Answer** | | **Value Q 2** | | |
|---|---|---|---|---|
| ≤ 15 | = | 0 | | |
| 16-30 | = | 1 | | |
| 31-60 | = | 2 | | |
| > 60 | = | 3 | | |
| | | | **Value Question 2** | **…….** |

Evaluate question 5a as follows:

| **Answer** | | **Value Q 5a** | | |
|---|---|---|---|---|
| Not at all (gar nicht) | = | 0 | | |
| Less than once (Weniger als einmal) | = | 1 | | |
| Once or twice (Ein- oder zweimal) | = | 2 | | |
| Three times or more (Dreimal oder häufiger) | = | 3 | | |
| | | | **Value Question 5a** | **…….** |

Add the point values of questions 2 and 5a as follows:

| **Sum Q 2 + 5a** | | **Value Q 2** | | |
|---|---|---|---|---|
| 0 | = | 0 | | |
| 1-2 | = | 1 | | |
| 3-4 | = | 2 | | |
| 5-6 | = | 3 | | |
| | | | **Component 2** | ……. |

**Third component: Duration of sleep:**

Evaluate question 4 as follows:

| **Answer** | | **Point value** | | |
|---|---|---|---|---|
| ≥ 7h | = | 0 | | |
| 6-7h | = | 1 | | |
| 5-6h | = | 2 | | |
| < 5h | = | 3 | | |
| | | | **Component 3:** | ……. |

**Fourth component: Efficiency of sleep:**

1. Go to question 4 and note the duration of sleep in hours ….h
2. Calculate the number of hours spent in bed (Bed laying hours):
   Waking up time (question 3):……
   Going to bed time (question 1):…
   Total No of hours in Bed: ….....h
3. Calculate the sleep efficiency /Quotient of sleep time and bed lying time) as follows:
   (sleeping time in hours/total hours spent in bed) X 100=…..%

| **Efficiency of sleep %** | | **Value of Component 4** | | |
|---|---|---|---|---|
| ≥ 85 | = | 0 | | |
| 75 -84 | = | 1 | | |
| 65-74 | = | 2 | | |
| < 65 | = | 3 | | |
| | | | **Component 4** | ……. |

**Fifth component: Sleep disturbances**

Evaluate question 5b-5j as follows:

| Answer | | Value Q 5a | | |
|---|---|---|---|---|
| Not at all (gar nicht) | = | 0 | | |
| Less than once (Weniger als einmal) | = | 1 | | |
| Once or twice (Einmal oder zweimal) | = | 2 | | |
| Three times or more (Dreimal oder häufiger) | = | 3 | | |
| | | | | |

Note the results of the questions 5b-5j and add the values. The resulting sum can vary from 0 to 27. It was originally divided into 4 groups.

| **Sum of questions 5b-5j** | | **Component 5 value** | | |
|---|---|---|---|---|
| 0 | = | 0 | | |
| 1-9 | = | 1 | | |
| 10-18 | = | 2 | | |
| 19-27 | = | 3 | | |
| | | | **Component 5** | **.....** |

## 5.4 Statistical analysis

The statistical analysis was performed using the SPSS-Software.

As statistical instrument the chi-square test and multi-variate analyses were chosen.

# 6 Results

## 6.1 Descriptive results

### 6.1.1 Number of patients/questionnaires

One thousand questionnaires were inserted in the periodical “Schmetterling” and sent to the members of the German self-help community by means of the routine distribution. 851 questionnaires were correctly completed and returned and could be included in this study.

### 6.1.2 General results

The disease was mostly diagnosed in women (94%).

The mean age of the patients was 48.7 years (8-87 years, Fig. 1).

Tab. 1: Gender of the patients

| | | N | % |
|---|---|---|---|
| Valid | Female | 800 | 94.0 |
| | Male | 51 | 6.0 |
| | Total | 851 | 100.0 |

Tab. 2: Age of the patients

| | | |
|---|---|---|
| N | Valid | 851 |
| | Missing | 0 |
| Mean | | 48.70 |
| Median | | 48.00 |
| Standard deviation | | 13.823 |
| Minimum | | 8 |
| Maximum | | 87 |

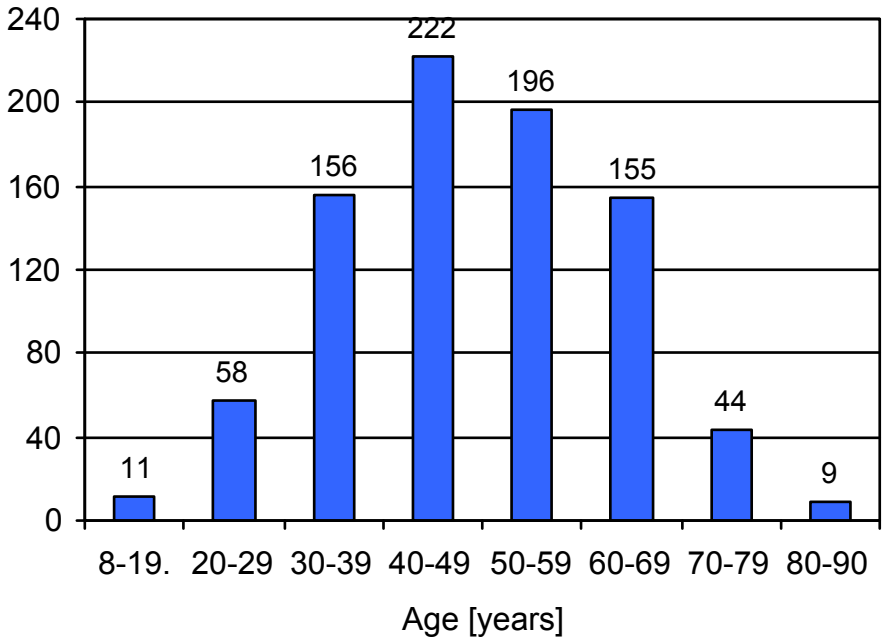


Fig. 1: Age distribution of the patients (n = 851)

It was noticed that the patients had a mean weight of nearly 70 kilograms and a height of nearly 167 cm. The BMI are seen in the table below (Tab. 3). The mean body mass index therefore lied in the upper normal range of 25.

Tab. 3: Anthropometric data

| | | Weight(kg) | Size (cm) | Body-Mass-Index (kg/m2) |
|---|---|---|---|---|
| N | Valid | 847 | 848 | 846 |
| | Missing | 4 | 3 | 5 |
| Mean | | 69.53 | 166.73 | 24.9567 |
| Median | | 67.00 | 166.00 | 24.1897 |
| Standard deviation | | 15.227 | 7.678 | 4.92657 |
| Minimum | | 22 | 120 | 13.52 |
| Maximum | | 175 | 196 | 59.85 |

### 6.1.3 Occupation status

Nearly 44% of the patients were pensioners and over 30% were employed and a few were unemployed or housewives, self-employed or students (Tab. 4, Fig. 2)

Tab. 4: Occupation status

| | | Frequency | % | Valid % |
|---|---|---|---|---|
| Valid | Student | 37 | 4.3 | 4.4 |
| | Pensioner | 373 | 43.8 | 44.0 |
| | Employee | 260 | 30.6 | 30.7 |
| | Worker | 28 | 3.3 | 3.3 |
| | Self-employed | 24 | 2.8 | 2.8 |
| | Umemployed/housewife | 126 | 14.8 | 14.9 |
| | Total | 848 | 99.6 | 100.0 |
| Missing | N.A. | 3 | 0.4 | |
| Total | | 851 | 100.0 | |

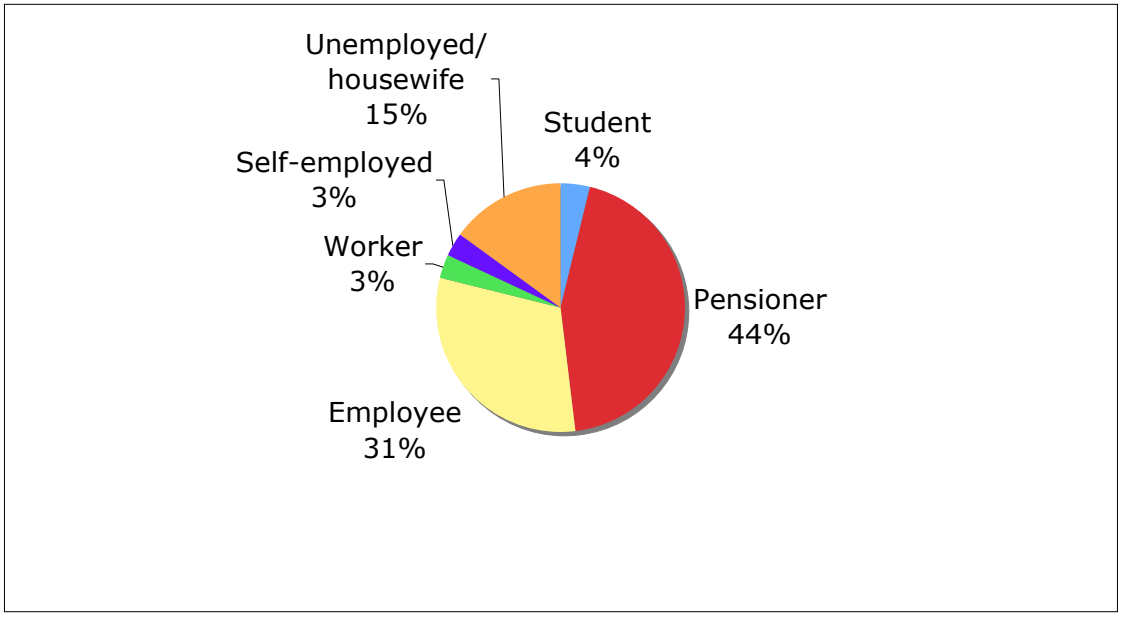


Fig. 2: Occupation status (n = 851)

### 6.1.4 Comorbidities newly diagnosed in 2005 as compared to data of 2004

In 2004, every patient suffered from a mean of three comorbid disorders (range 0-14). In 2005, for each patient, a mean of two additional comorbities (0-11) was reported (Tab. 5).

Tab. 5: Count of Comorbities

| | | Number of comorbities Ever (data of 2004) | Number of comorbities New (2005) |
|---|---|---|---|
| N | Valid | 824 | 849 |
| | Missing | 27 | 2 |
| Mean | | 3.37 | 1.29 |
| Median | | 3.00 | 1.00 |
| Standard deviation | | 2.469 | 1.857 |
| Minimum | | 0 | 0 |
| Maximum | | 14 | 11 |

Some patients, in 2005, had 1 to 4 accompanying diseases or comorbidities such as osteoarthritis (18.8%), osteoporosis (12.5%), hypertension (11.6%). Mental-health problems or depression were seen in 11% of the cases and scarring skin diseases in 10.9%. Other diseases like chronic obstruction of the airways, fibromyalgia, tumours, diabetes were also observed in a minority of the patients (Tab. 6). In comparison, the most frequently reported comorbidities of the former LuLa study were hypertension 33%, scarring skin disease 24.4%, osteoarthritis (25.2%), osteoporosis (24%), mental-health problems/depression (22.9%) and chronic renal disease (22%). Some cases showed thrombo-embolic events, myocardiac infarcts and stroke (Fischer-Betz et al. 2005).

Tab. 6: Type of comorbities in 2004 (n = 824) and 2005 (n = 849)

| | New (2005) | | Ever (data of 2004) | |
|---|---|---|---|---|
| | N | % | N | % |
| Essential hypertension | 98 | 11.6% | 328 | 39.8% |
| Chronic renal failure | 46 | 5.4% | 167 | 20.3% |
| Diabetes mellitus | 12 | 1.4% | 48 | 5.8% |
| Neoplasms | 15 | 1.8% | 51 | 6.2% |
| Chronic respiratory disorder | 68 | 8.0% | 187 | 22.7% |
| Chronic hepatic disorder | 35 | 4.1% | 50 | 6.1% |
| Chronic gastrointestinal disorder | 59 | 7.0% | 151 | 18.3% |
| Lipid metabolic disorder | 103 | 12.2% | 283 | 34.3% |
| Psychiatric disorder/depression | 93 | 11.0% | 241 | 29.2% |
| Arthrosis | 159 | 18.8% | 289 | 35.1% |
| Scarring dermal lesions | 92 | 10.9% | 182 | 22.1% |
| Osteoporosis | 106 | 12.5% | 216 | 26.2% |
| Fibromyalgia | 57 | 6.8% | 116 | 14.1% |
| Thrombosis/embolism | 44 | 5.2% | 160 | 19.4% |
| Abortion last year | 53 | 6.7% | 127 | 15.4% |
| Menopause before the age of 40 | 53 | 6.7% | 104 | 12.6% |

## 6.2 Descriptive analysis of sleep

Sleep was studied in different single components when analysing the answers to the questions 1-11 on the pages 3 and 4 of the Questionnaire: “LuLa Fragebogen 2005”.

### 6.2.1 Sleep quality

More than half of the patients mentioned sleep was fairly good or very good in the past 4 weeks (Tab. 7, Fig. 3).

Tab. 7: Sleep quality last 4 weeks (n = 846)

| | | N | % | Valid % |
|---|---|---|---|---|
| Valid | Very good | 74 | 8.7 | 8.7 |
| | Fairly good | 416 | 48.9 | 49.2 |
| | Fairly bad | 309 | 36.3 | 36.5 |
| | Very bad | 47 | 5.5 | 5.6 |
| | Total | 846 | 99.4 | 100.0 |
| Missing | | 4 | 0.5 | |
| | System | 1 | 0.1 | |
| | Total | 5 | 0.6 | |
| Total | | 851 | 100.0 | |

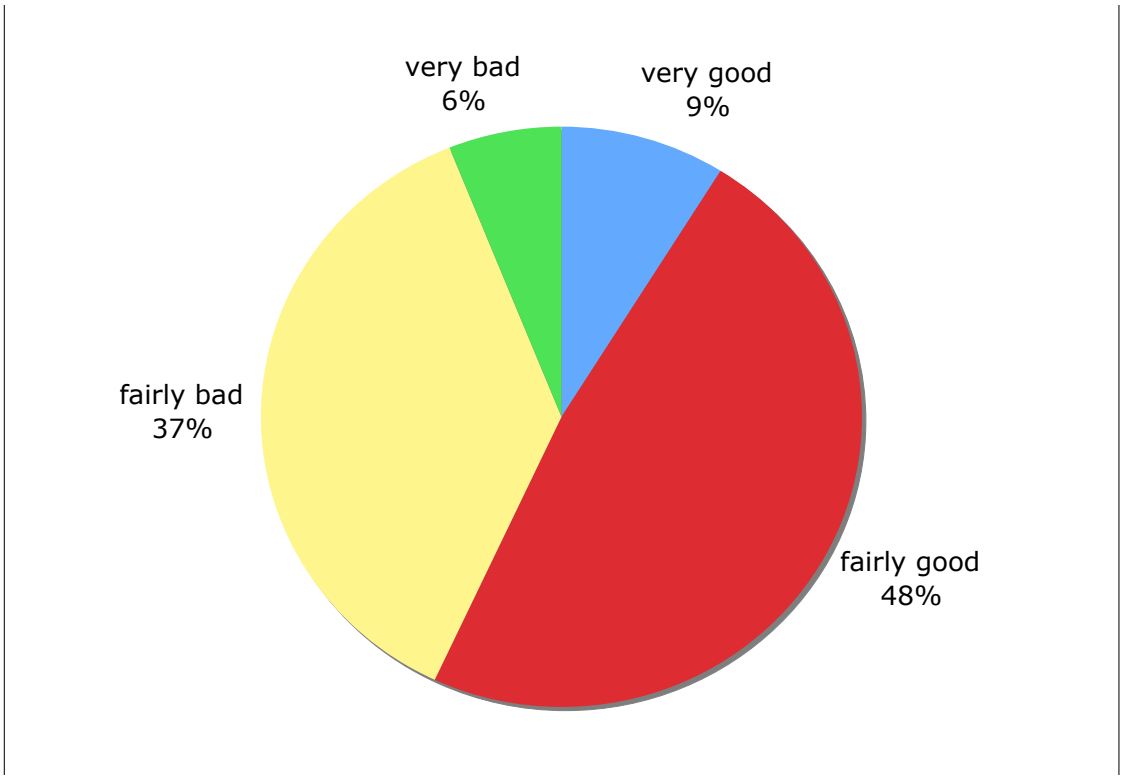


Fig. 3: Quality of sleep (n = 846)

### 6.2.2 Sleep medication

More than 80% never needed any sleeping pills over the same period of time.(Tab8, fig 4).

Tab. 8: Sleeping pills last 4 weeks (n = 846)

| | | N | % | Valid % |
|---|---|---|---|---|
| Valid | Not at all | 694 | 81.6 | 82.0 |
| | Sometimes | 66 | 7.8 | 7.8 |
| | Often | 36 | 4.2 | 4.3 |
| | Three or more times a week | 50 | 5.9 | 5.9 |
| | Total | 846 | 99.4 | 100.0 |
| Missing | N.A. | 3 | 0.4 | |
| | System | 2 | 0.2 | |
| | Total | 5 | 0.6 | |
| Total | | 851 | 100.0 | |

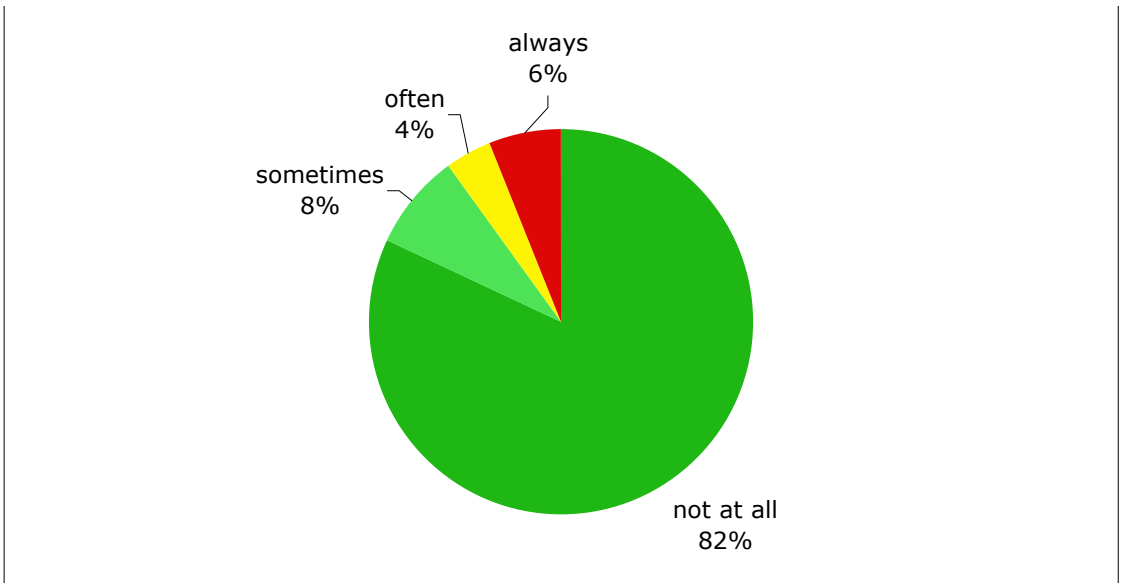


Fig. 4: Intake of sleeping medication in the past 4 weeks (n = 846)

### 6.2.3 Effective sleeping time and sleep efficiency

As for question 4, the mean effective sleeping time was 6.8 hours (±1.4) while the sleep efficiency was nearly 80% (Tab. 9).

Tab. 9: Sleep efficiency (%)

| | | |
|---|---|---|
| N | Valid | 847 |
| | Missing | 4 |
| Mean | | 79.4000 |
| Median | | 80.0000 |
| Standard deviation | | 16.37140 |
| Minimum | | 30.00 |
| Maximum | | 169.28 |

### 6.2.4 Reasons for sleep disturbances

The patients were disrupted in sleep in nearly 25% of the cases because they always had to go to the toilet (Tab. 10). However in less than 6% of the cases patients were always woken up by pain. Surprisingly half of the patients did not say pain was one of the reasons ever to have disturbed their sleep. In over 30% of the cases, the patients said they often woke up in the middle of the night or early in the morning. And more than 80% said that breathing problems were never the cause to disrupt their sleep.

Tab. 10: Stated reasons for sleep disturbances (multiple answers were permitted)

| | **Never** | | **Sometimes** | | **Often** | | **Always** | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Cannot go to sleep within 30 minutes | 280 | 33.8% | 266 | 32.1 | 171 | 20.7 | 111 | 13.4 |
| Wake up in the middle of night/early morning | 155 | 18.6 | 263 | 31.5 | 266 | 31.9 | 151 | 18.1 |
| Have to get up to use the bathroom | 166 | 19.7 | 269 | 31.9 | 201 | 23.8 | 207 | 24.6 |
| Cannot breathe comfortably | 669 | 80.5 | 114 | 13.7 | 41 | 4.9 | 7 | .8 |
| Cough or loud snoring | 560 | 67.5 | 182 | 21.9 | 68 | 8.2 | 20 | 2.4 |
| Feel too cold | 500 | 60.3 | 228 | 27.5 | 85 | 10.3 | 16 | 1.9 |
| Feel too warm | 509 | 61.5 | 223 | 27.0 | 75 | 9.1 | 20 | 2.4 |
| Had bad dreams | 478 | 57.4 | 257 | 30.9 | 82 | 9.8 | 16 | 1.9 |
| Have pain | 370 | 46.5 | 252 | 31.7 | 127 | 16.0 | 47 | 5.9 |
| Other reasons | 83 | 20.1 | 125 | 30.3 | 148 | 35.9 | 56 | 13.6 |

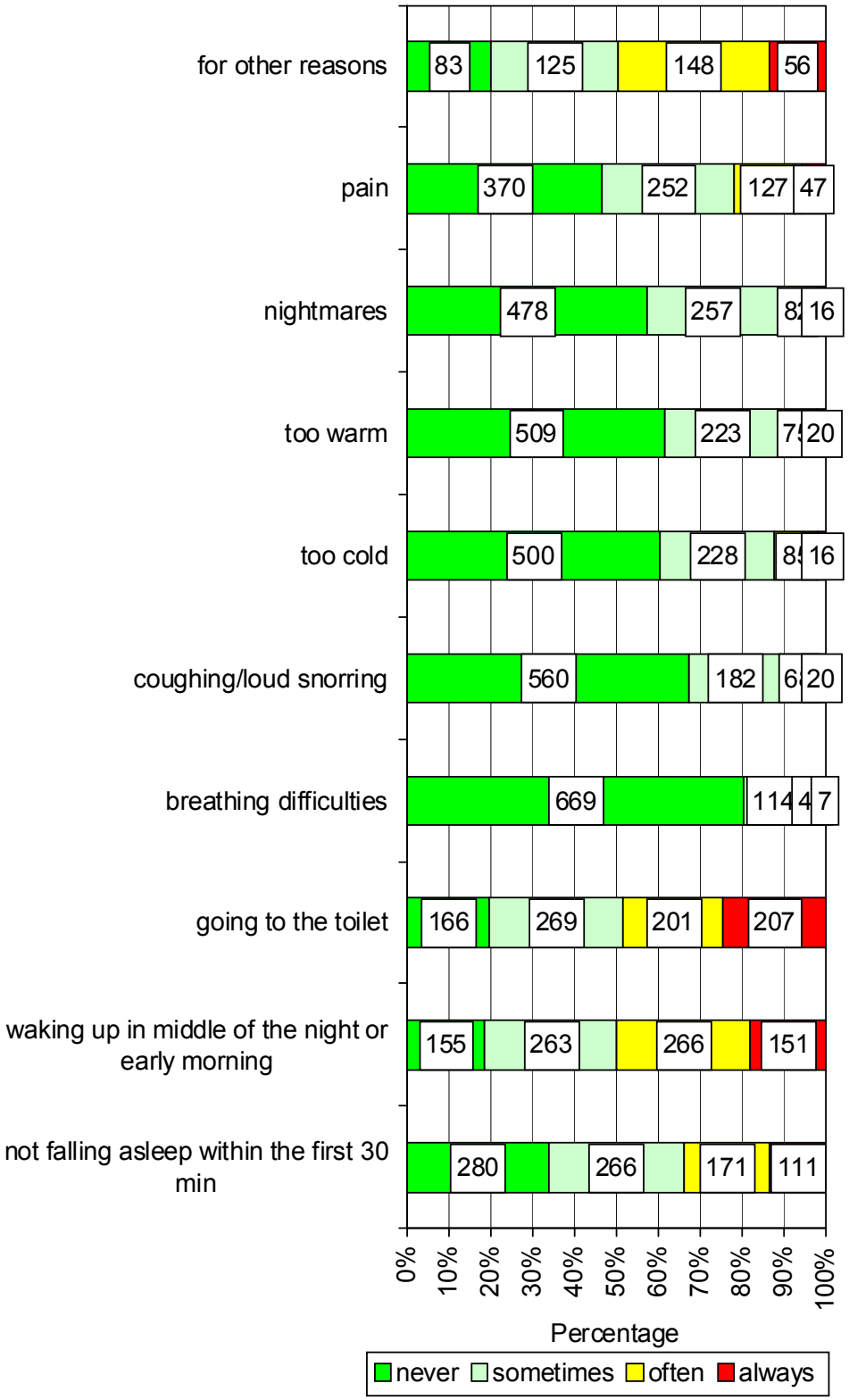


Fig. 5: Reasons of sleep disturbance (Multiple reasons possible)

### 6.2.5 Comments of the roommates about the patients' sleep

In order to analyze sleep, it is important to observe the patients while they are asleep. This can only be done by someone who sleeps next to the patient or at least lives in the same household. More than half of the patients did not sleep alone in the room and only about 17% lived alone in their housing (Tab. 11). Only 17% of our patients did not have any room/flat-mates. Therefore, the following comments of these room/flat-mates may be very relevant for our study.

Tab. 11: Bed partner or roommate of 846 patients

| | | N | % | Valid % |
|---|---|---|---|---|
| Valid | No bed partner or roommate | 373 | 43.8 | 44.1 |
| | Partner in same room, but not same bed | 187 | 22.0 | 22.1 |
| | Partner/roommate in other room | 138 | 16.2 | 16.3 |
| | No, single living | 148 | 17.4 | 17.5 |
| | Total | 846 | 99.4 | 100.0 |
| Missing | | 2 | 0.2 | |
| | System | 3 | 0.4 | |
| | Total | 5 | 0.6 | |
| Total | | 851 | 100.0 | |

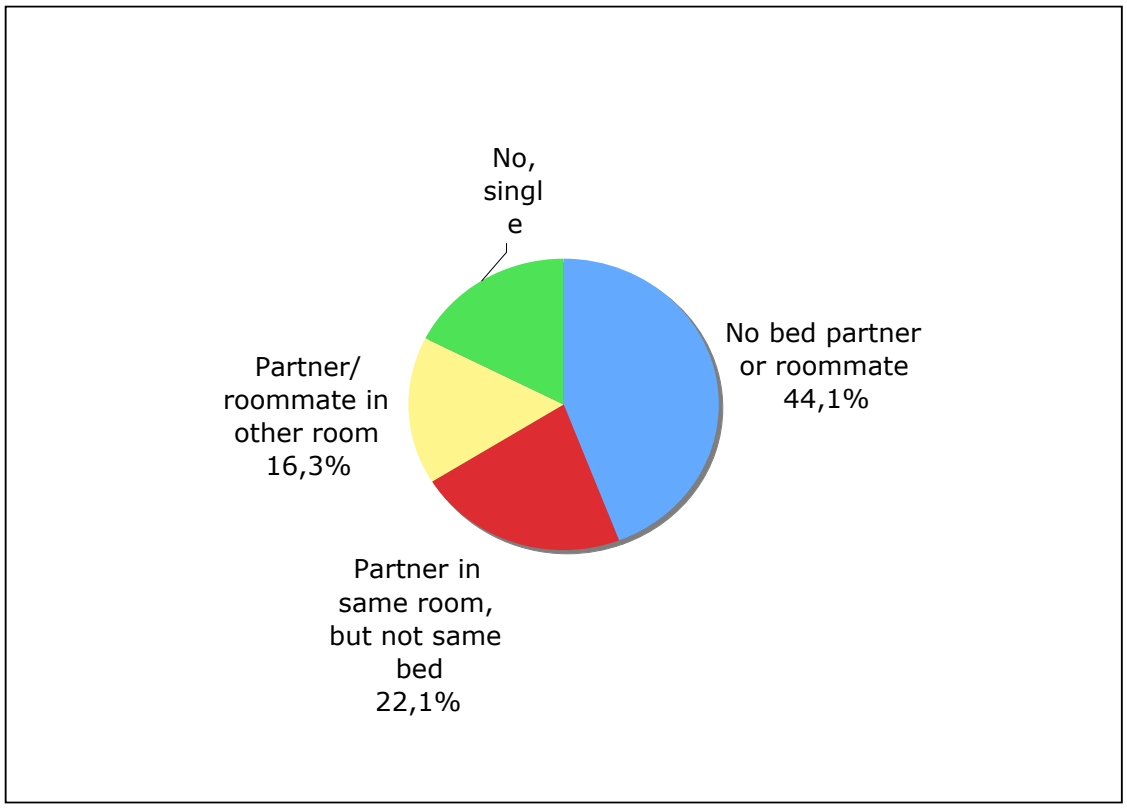


Fig. 6: Roommate

Loud snoring was often heard by the room-mate in 14.1% of the cases, nervous leg movements in 10.9% of the cases. Long breathing pauses and confusional state were near to never felt by the partners (87.9% and 84.9%).

Tab. 12: Comments of the roommates about the patient

| | Never | | Sometimes | | Often | | Always | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| ...loud snoring | 297 | 44.4% | 238 | 35.6% | 94 | 14.1% | 40 | 6.0% |
| ...long breathing pauses | 569 | 87.9% | 57 | 8.8% | 18 | 2.8% | 3 | 0.5% |
| ...legs twitching or jerking | 376 | 57.1% | 196 | 29.7% | 72 | 10.9% | 15 | 2.3% |
| ...confusion/disorientation | 544 | 84.9% | 62 | 9.7% | 27 | 4.2% | 8 | 1.2% |

### 6.2.6 Pittsburg Sleep Quality Index (PSQI)

The distribution of PSQI scores is shown in 7. The mean PSQI score was 7.35 points with a range of value from 0 to 19 points (Tab. 13).

Tab. 13: Pittsburg Sleep Quality Index (PSQI)

| | | |
|---|---|---|
| N | Valid | 851 |
| | Missing | 0 |
| Mean | | 7.35 |
| Median | | 7.00 |
| Standard deviation | | 3.819 |
| Minimum | | 0 |
| Maximum | | 19 |

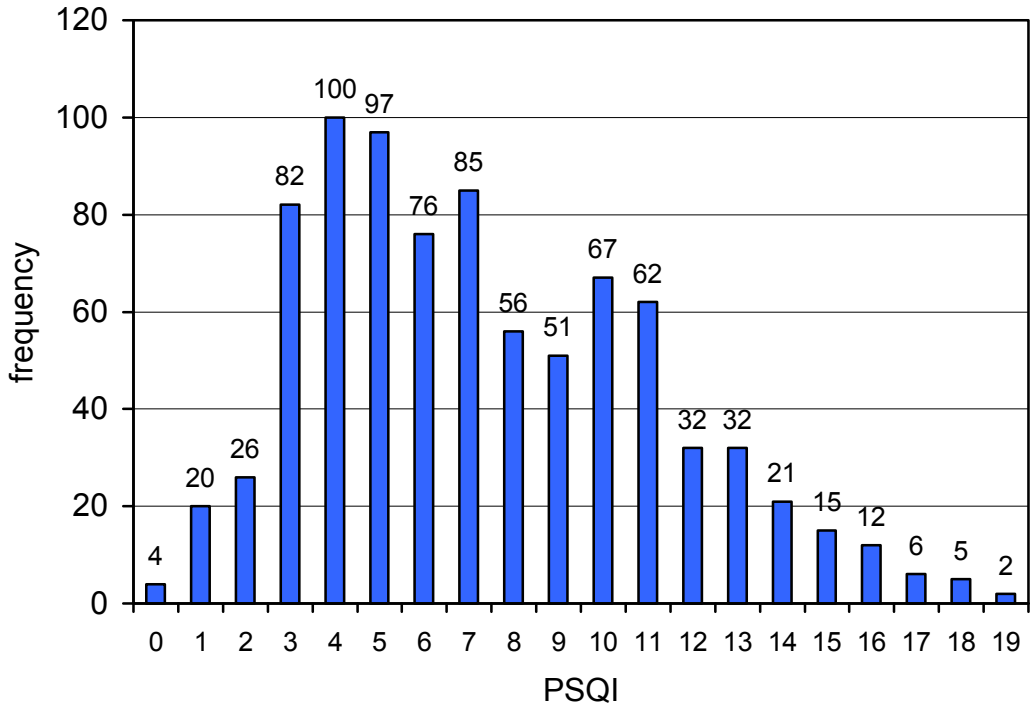


Fig. 7: PSQI

According to Buysse, the PSQI score can further be subdivided into three categories:

- Patients who suffer from no sleep disturbance (good sleepers; sum of points not more than 5)
- Those who complain of slight or moderate sleep disturbance (scores between 6-10)
- Chronic and severe sleeping disorder (scores over 10)

The PSQI analysis showed that 38.7% of all patients had an undisturbed sleep and light sleep disorders existed in 39.4%. 22.0% of the patients suffered from chronic sleep disorders (Tab. 14).

Tab. 14: Total PSQI (categories)

| | N | % |
|---|---|---|
| Quiet sleep | 329 | 38.7 |
| Slight sleep disorder | 335 | 39.4 |
| Chronic sleep disorder | 187 | 22.0 |
| Total | 851 | 100.0 |

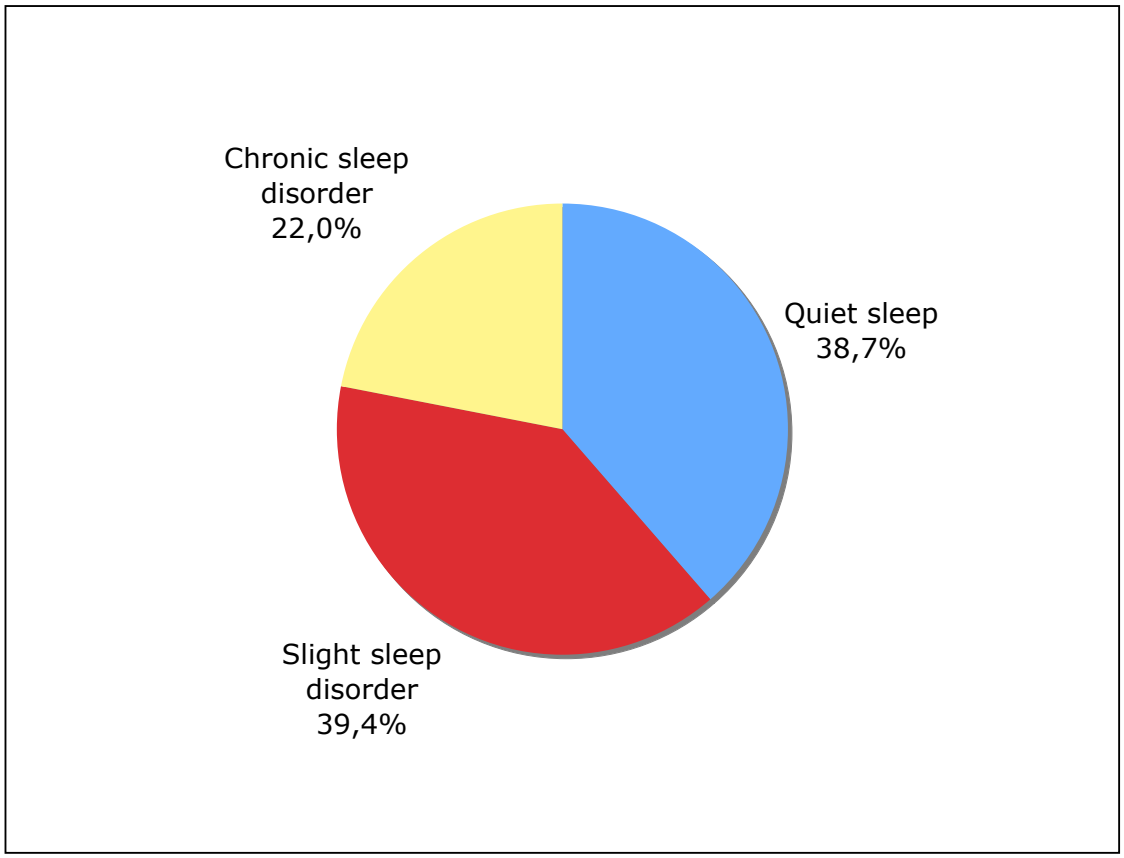


Fig. 8: Distribution of patients on three PSQI-categories

## 6.3 Statistical Analysis of the results – univariate analysis

### 6.3.1 Correlation of sleep disturbance with the age of the patients

The extent of sleep disturbances in SLE patients increased highly signicifant with growing age (chi-square: 15.9163, $P \leq 0001$).

Tab. 15: Correlation of sleep disturbance with the age of the patients

| PSQI (total) grouped | Age of the patients | | | | | |
|---|---|---|---|---|---|---|
| | N | Mean | Std. dev. | Median | Min | Max |
| Healthy sleep | 329 | 45.653 | 13.544 | 44 | 10 | 87 |
| Slight sleep disturbance | 335 | 49.096 | 13.959 | 50 | 8 | 82 |
| Chronic sleep disturbance | 187 | 53.358 | 12.7 | 53 | 22 | 81 |

### 6.3.2 Correlation of sleep disturbance with the intake of certain medication

Generally, the intake of any medication was correlated with sleep disturbance (P=0.0058). In the following we analyse the correlation between certain medications and sleep disturbance separately.

NSAR

The quality of sleep of the patients that took NSAR was clearly worse than that of the patients that did not take any medication. In this way, 32.7% of the patients that took NSAR suffered from chronic sleep disturbance while there were only 18.5% of patients without a NSAR intake which had the same problems (Fig.9).

On the other hand, only 25.0% of the patients who took NSAR had a healthy sleep and as much as 43.1% of those who did not. So, this general correlation between intake of medication and quality of sleep was highly significant ($p<0.0001$).

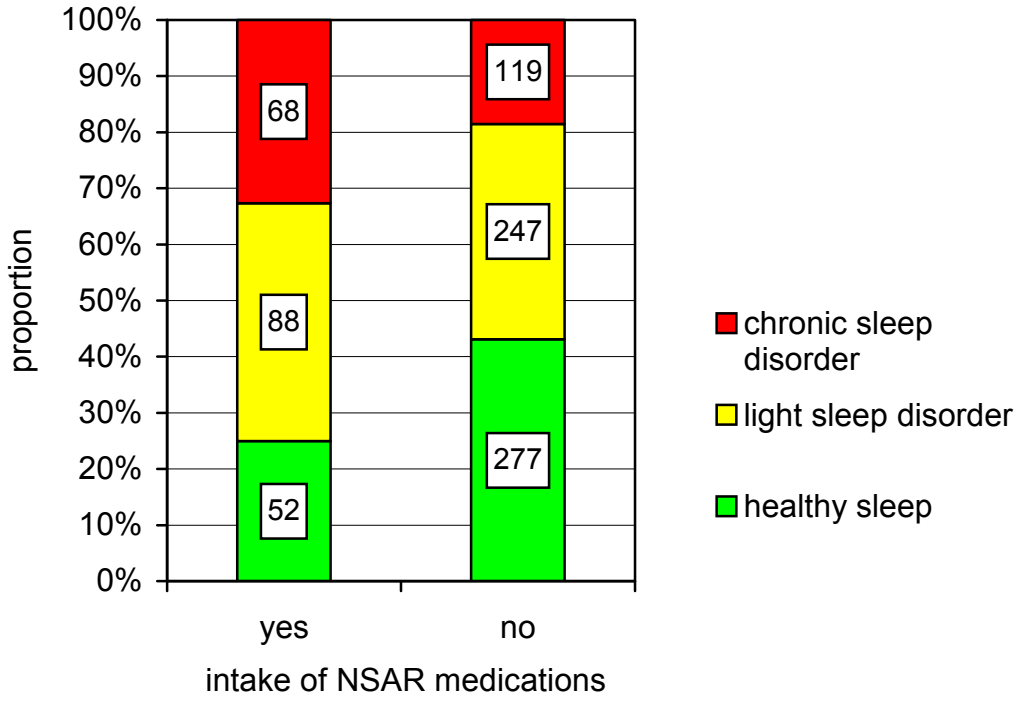


Fig. 9: Sleep disturbance and the intake of NSAR

Steroids over 7.5

Over 30% of the patients using steroids in dosages higher than 7.5 mg had chronic sleep disturbance in comparison with 20% of those patients who are not using steroids. Patients using steroids in smaller dosage (less than 7.5 mg) did not show this correlation (Fig. ).

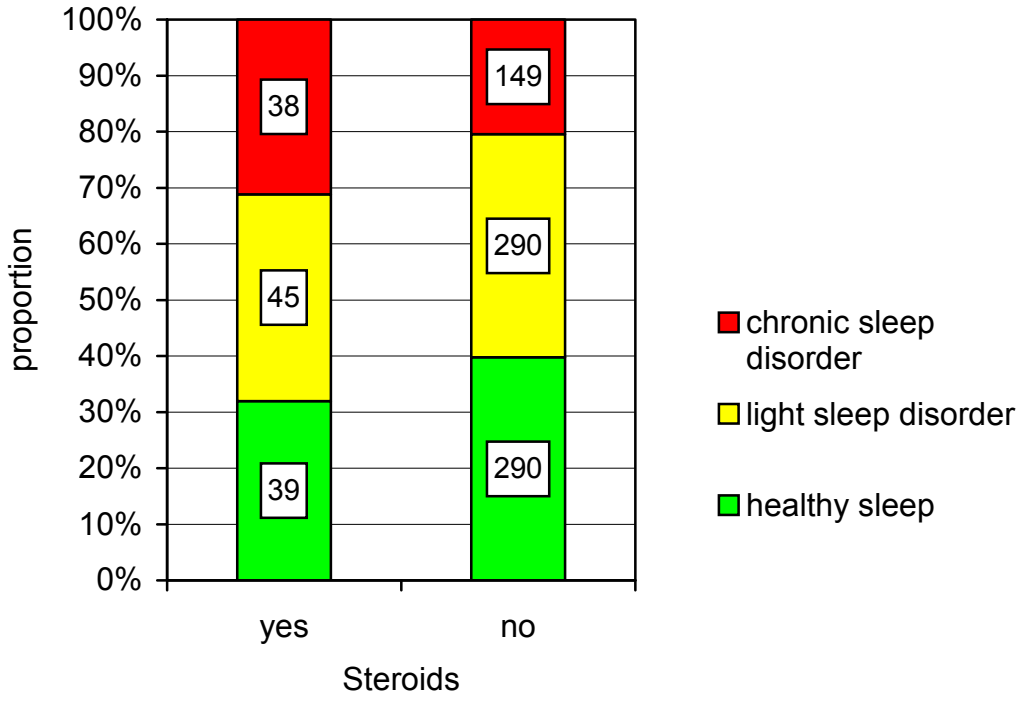


Fig. 10: Sleep disturbance and an intake of steroids higher than 7.5

Medication for osteoporosis

Slight differences in the frequency of sleep disturbance are also obvious in relation to the osteoporosis medication: A chronic sleep disturbance was more often in those using an osteoporosis medication while more than 40% of the non-users showed a healthy sleep as compared to 33% of the users (Fig.11).

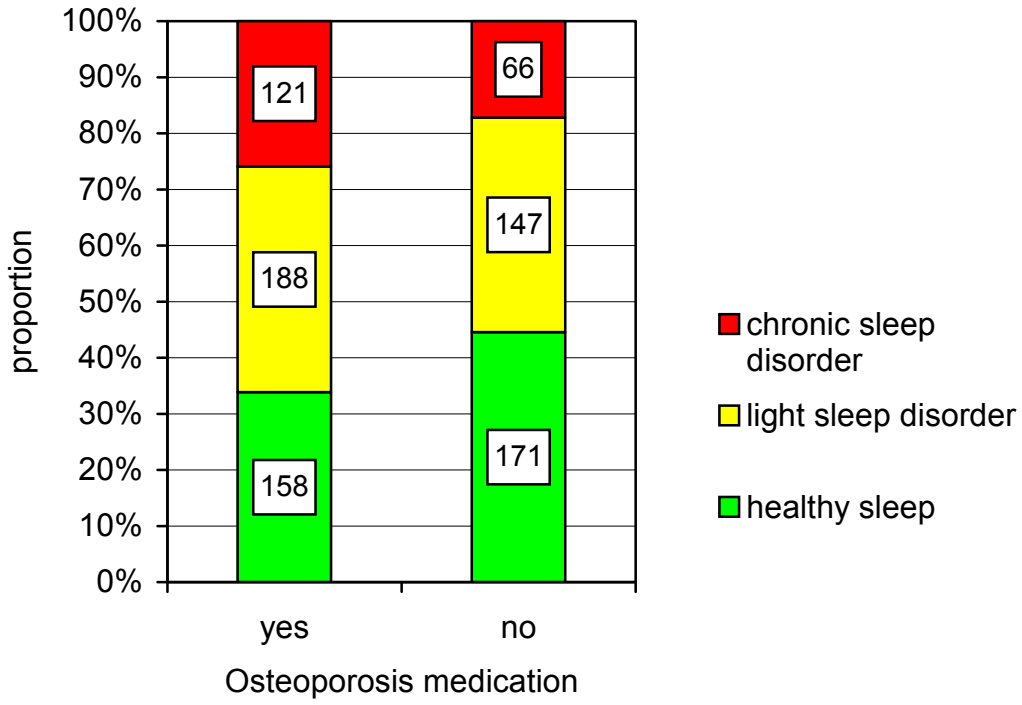


Fig. 11: Sleep disturbance and the intake of osteoporosis medication

**Blood pressure or heart medication**

Similar results are seen with these medications too. Nearly 30% of the patients taking this type of medication suffered from chronic sleep disturbance in comparison to nearly 17% of those not taking the medication.

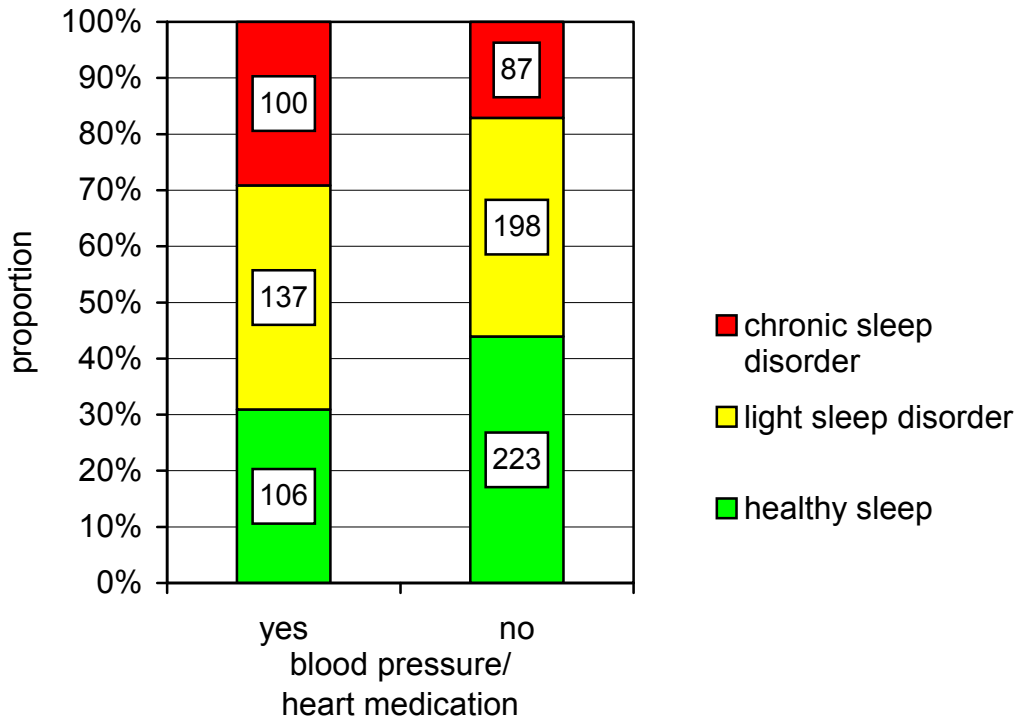


Fig. 12: Sleep disturbance and blood pressure/heart medication

Analgesics and pain killers

The difference between the patients taking analgesics and those who don't is clear as nearly 40% of those who take it suffer from chronic sleep disturbance in comparison to less than 20% of those who don't. And over 40% of those who don't take them benefit from healthy refreshing sleep while this is only the case in 22.8% of those who take pain killers which is a significant difference (Fig.13).

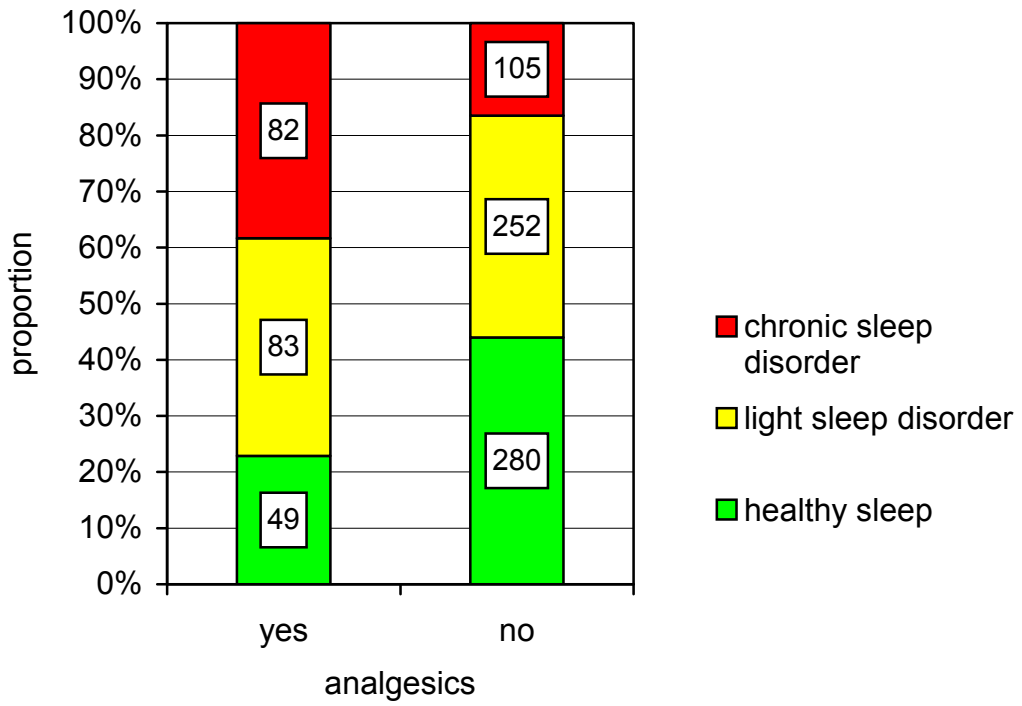


Fig. 13: Sleep disturbance and the use of analgesics

Psychopharmaca and antidepressives

Over 40 % of the patients using this type of medication have chronic sleeping problems which is only the case in less than 20% of those who don't. On the other hand, over 40% of the patients who don`t need this medication sleep well and only 20% have sleep disturbances (Fig. 14).

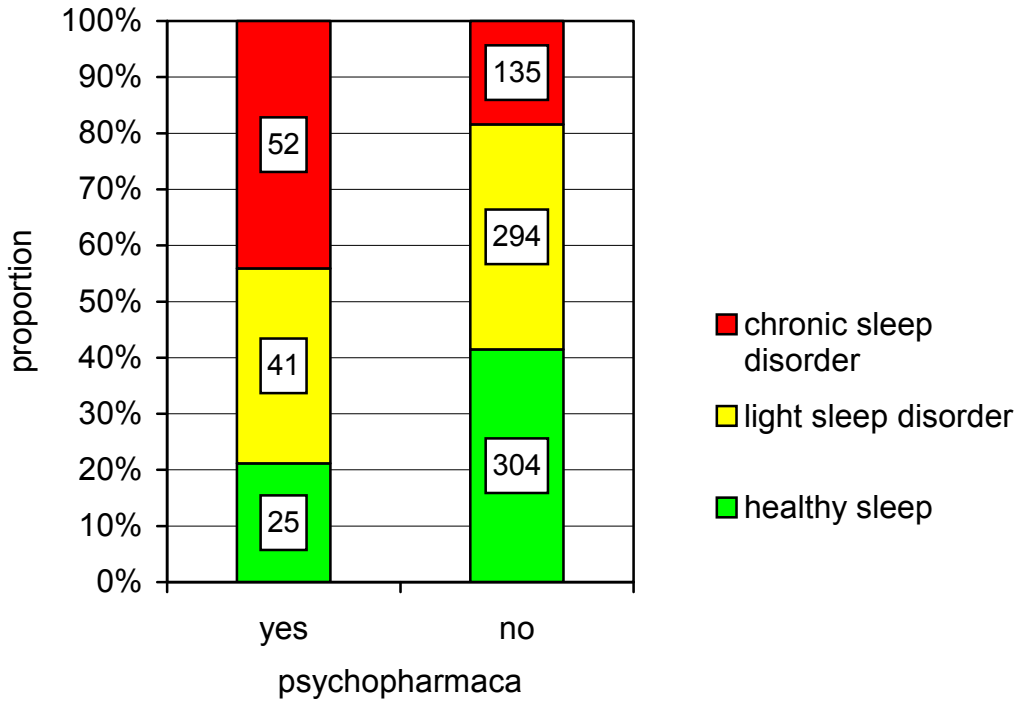


Fig. 14: Sleep disturbance and the use of psychopharmaca

Medication for gastrointestinal disorders

Within the group of patients with a gastric medication, 31.3% suffer from a chronic sleep disorder and only 26.0 have a healthy sleep. In contrast, from the patients without such a medication, not more than 17.8% have a chronic sleep disturbance but 44.4% slept well (Fig.15).

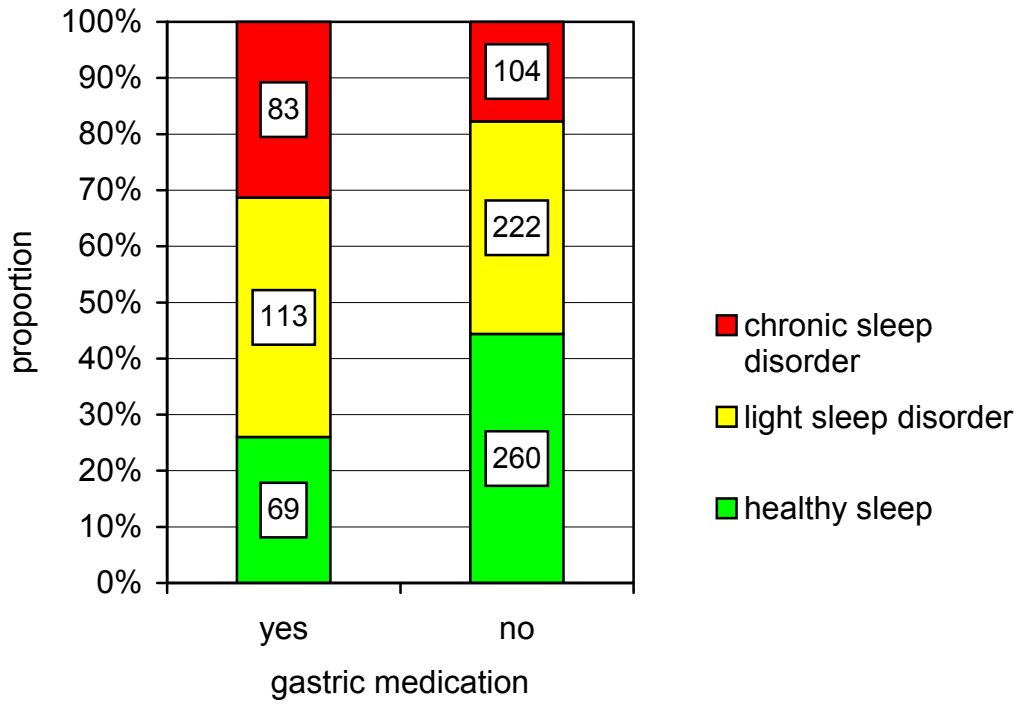


Fig. 15: Sleep disturbance and the use of gastric medication

Medication treating accompanying dermal disease

The differences between patient with or without a dermal medication are slightly: A chronic sleep disorder is found in 25.6% of users and 18.5 of non-users and a healthy sleep is reported in 35.0% of users and 43.6% of non-users (Fig.16).

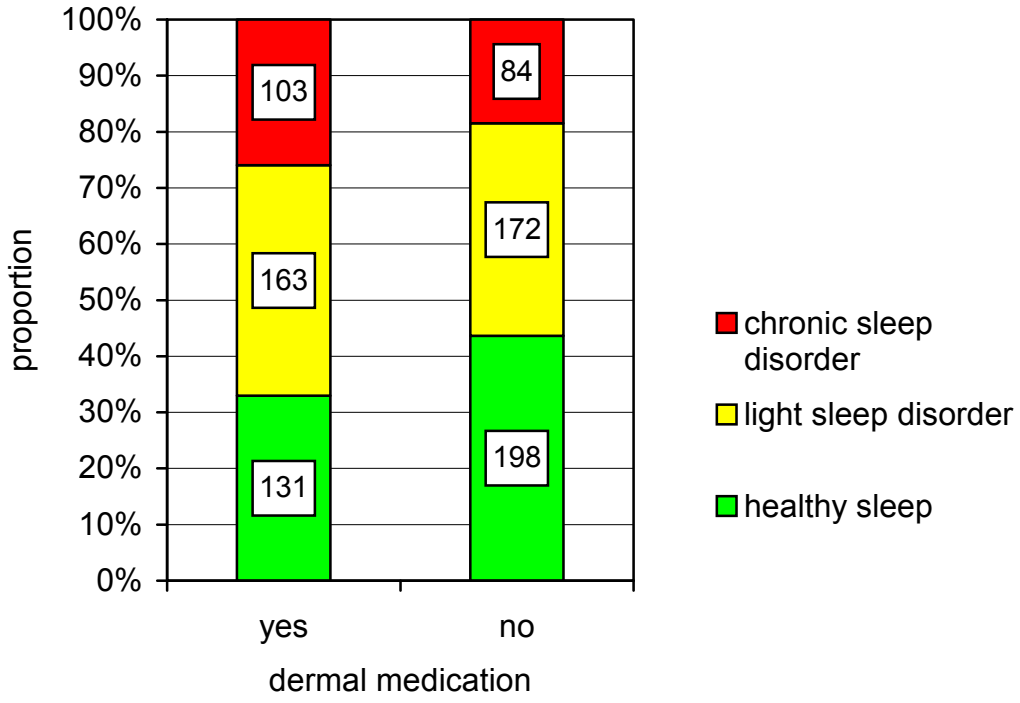


Fig. 5: Correlation of sleep disturbance with dermal medication

Alternative medicine

Even alternative medicine showed slight differences in favour of the patients who don't take them with regard to healthy sleep (Fig 17).

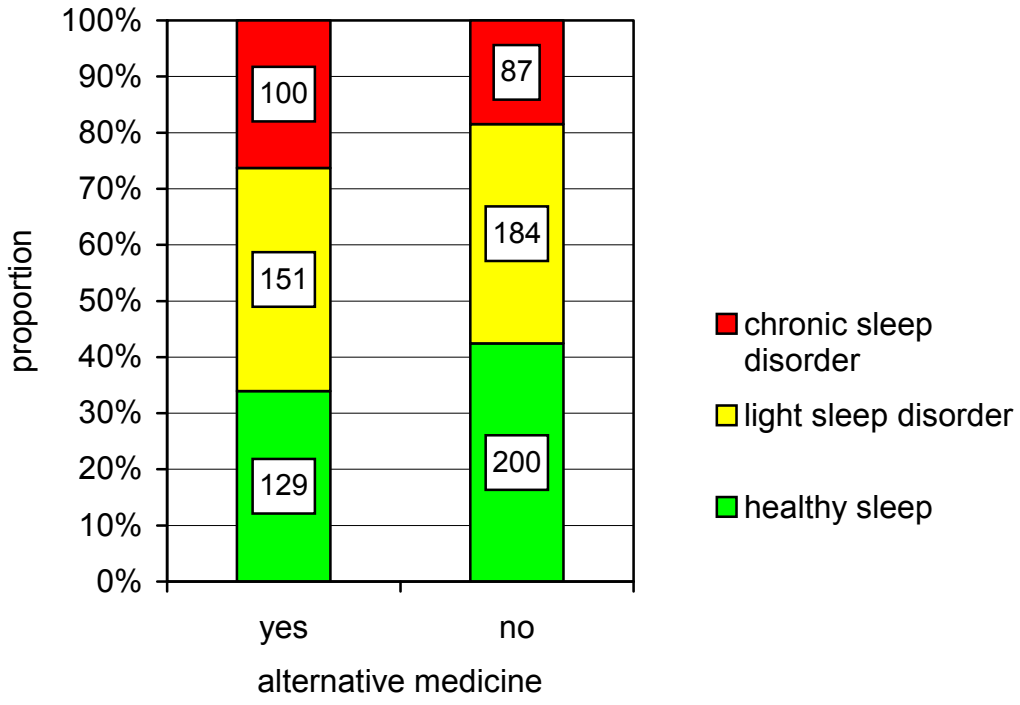


Fig. 17: Sleep disturbance and the use of alternative medicine

### 6.3.3 The correlation of sleep and perceived pain

Pain was found to have a high correlation with the sleep disturbance in SLE (Chi-square 46.3407, $P \leq 0001$). In patients with a healthy sleep the mean pain score was $2.0 \pm 2.0$ and in patients with chronic sleep disorders $4.8 \pm 2.6$ (Tab. 16).

Tab. 16: Correlation of sleep disturbance with perceived pain

| PSQI (total) grouped | Pain in the last 7 days (Scale 0-10) | | | | | |
|---|---|---|---|---|---|---|
| | N | Mean | Std dev. | Median | Min | Max |
| Healthy sleep | 328 | 1.9848 | 1.9683 | 2 | 0 | 9 |
| Slight sleep disturbance | 333 | 3.5135 | 2.5097 | 3 | 0 | 10 |
| Chronic sleep disturbance | 187 | 4.8396 | 2.5665 | 5 | 0 | 10 |

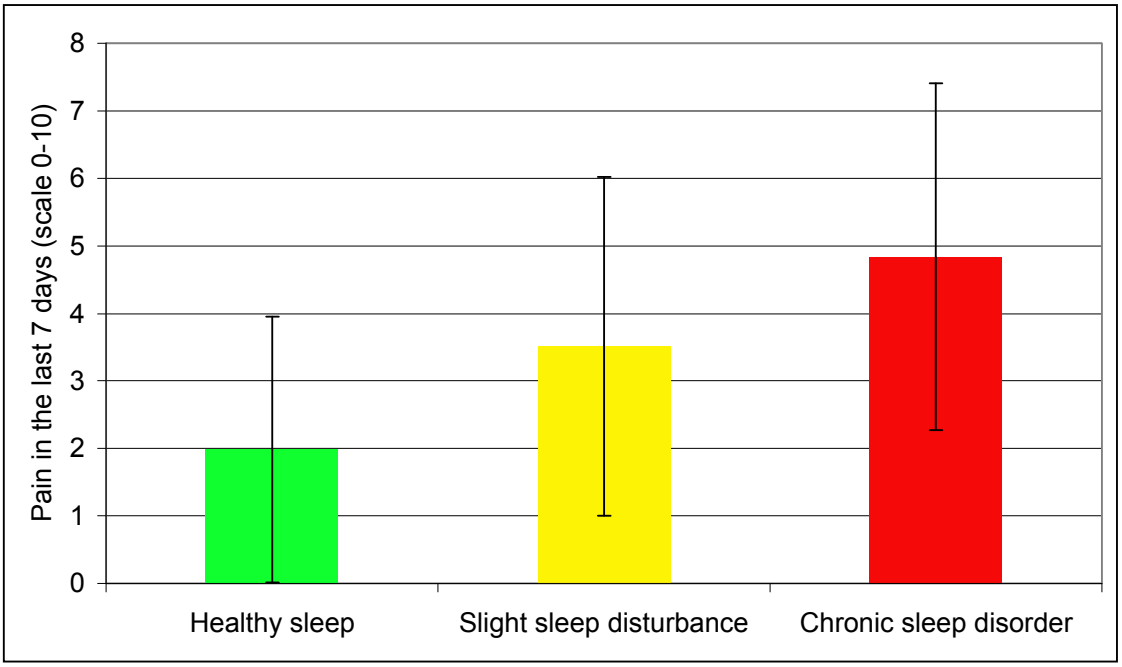


Fig. 68: Correlation between sleep and pain

### 6.3.4 The correlation of sleep and SLE comorbidities or accompanying diseases

The presence of accompanying diseases did not show any significant correlation but when cut into the main comorbidities, we found some results.

Hypertension correlated significantly with sleep disturbance (Chi-square: 7.3885, significance P = 0.0066) (Fig.19).

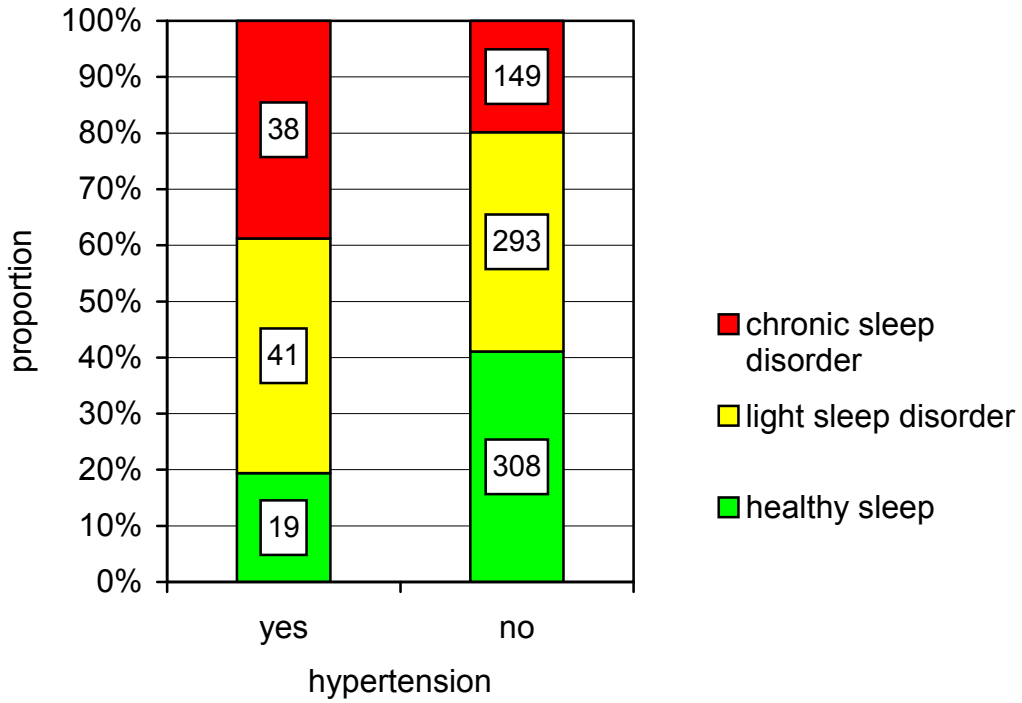


Fig. 79: Sleep disturbance and hypertension

Diabetes did not seem to be significantly correlating with sleep disturbance (P= 0.458)

Tumors did not show any relation to the sleeping problems in SLE (P= 0.7133).

Asthma and breathing problems were a significant reason for sleep interruption (P= 0.0348). A healthy sleep was seen to occur in 25.0% of patients with an accompanying chronic respiratory disorder but in 39.9% without such problems. Otherwise, chronic sleep disorders were found in 29.4% with and 21.1% without asthma or breathing difficulties (Fig.20).

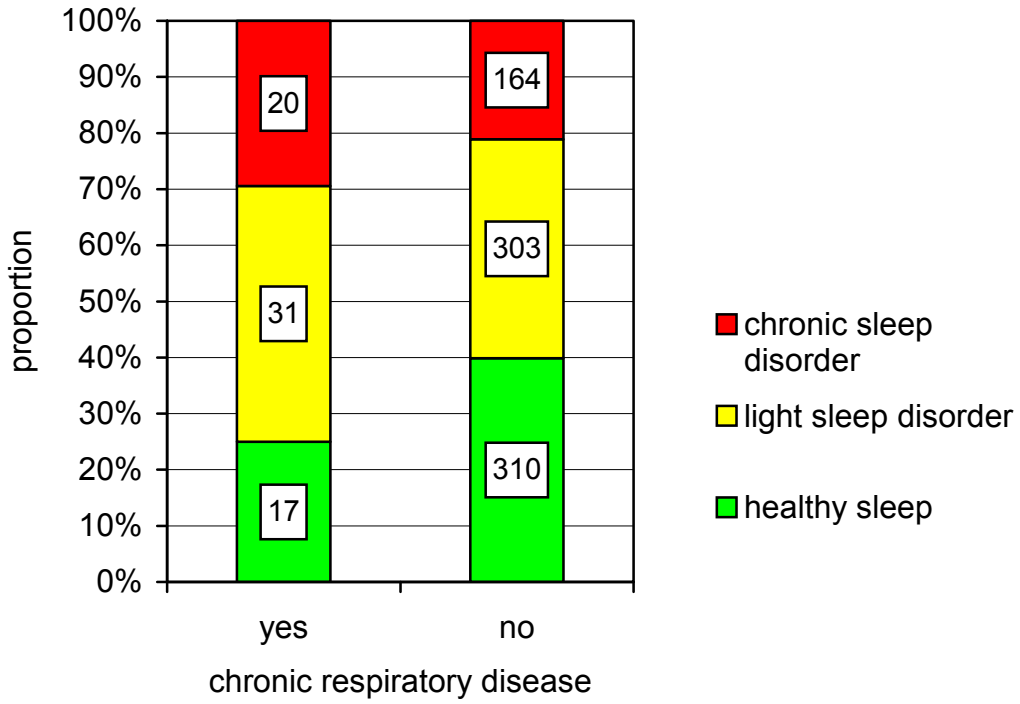


Fig.20: Sleep disturbance and chronic respiratory disease

A significant correlation was also seen in relation to chronic liver disease. More patients with hepatic disease were poor sleepers (Fig.21).

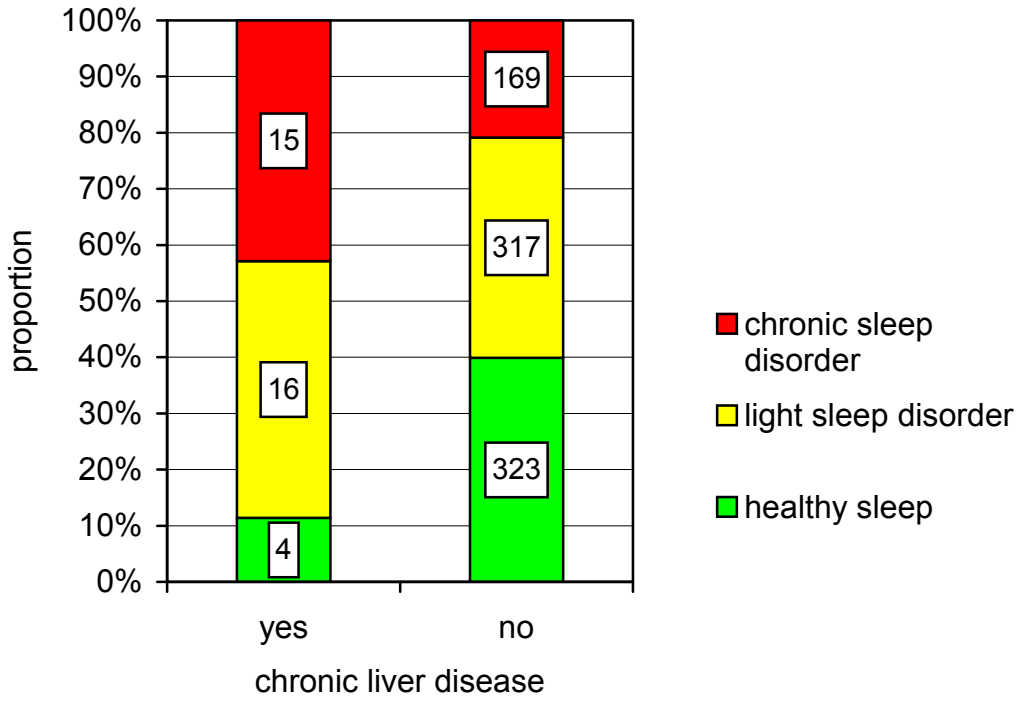


Fig.21: Sleep disturbance and chronic liver disease

Good sleepers were clearly more among the patients without gastrointestinal problems (Fig.22).

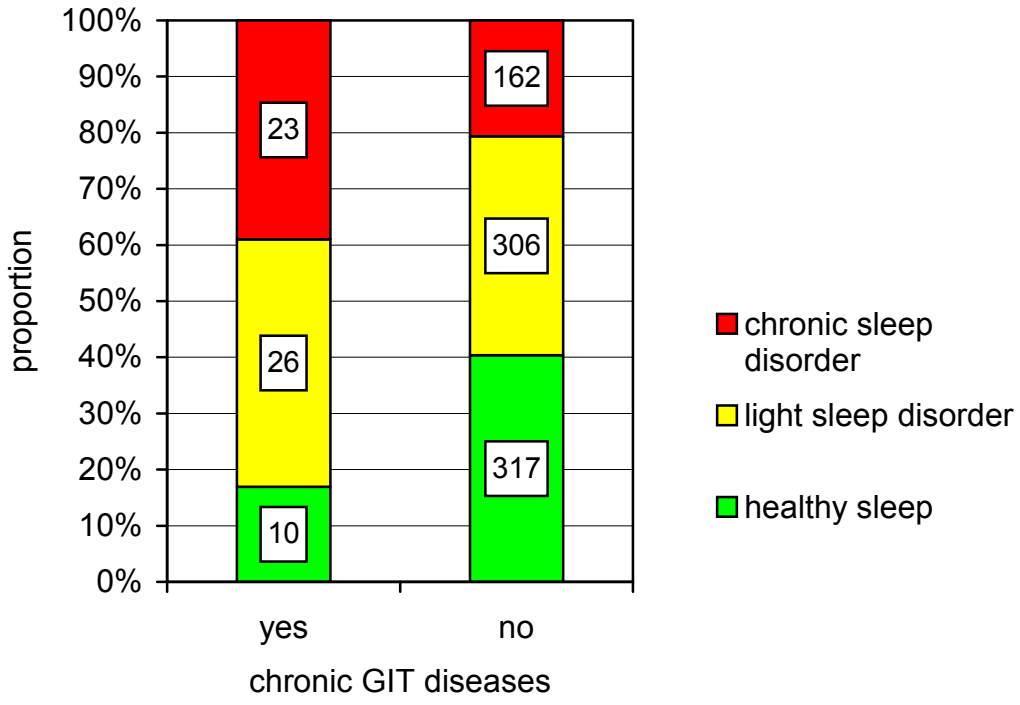


Fig.22: Sleep disturbance and chronic gastrointestinal diseases

In patients with disorders of the fat metabolism, poor sleepers were slightly more represented (36.9%) than good sleepers (28.2%). In patients without such problems 40.2% had a healthy sleep and only 19.8% chronic disturbances (Fig.23).

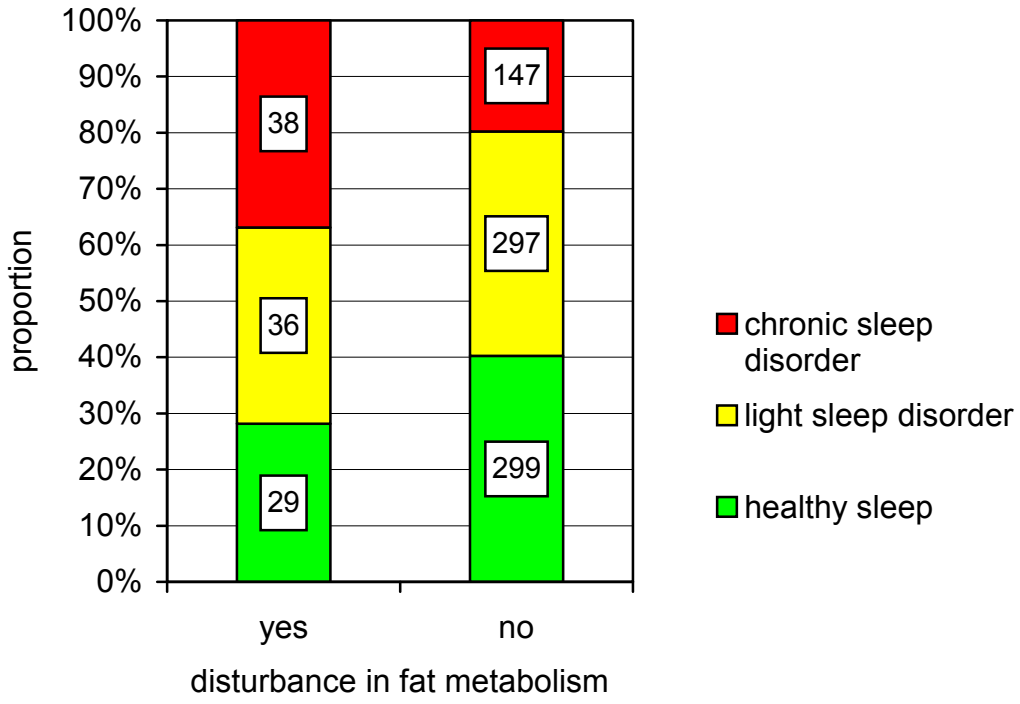


Fig.23: Sleep disturbance and disturbance in fat metabolism

Good sleepers are more often among SLE patients without mental health problems (Fig.24).

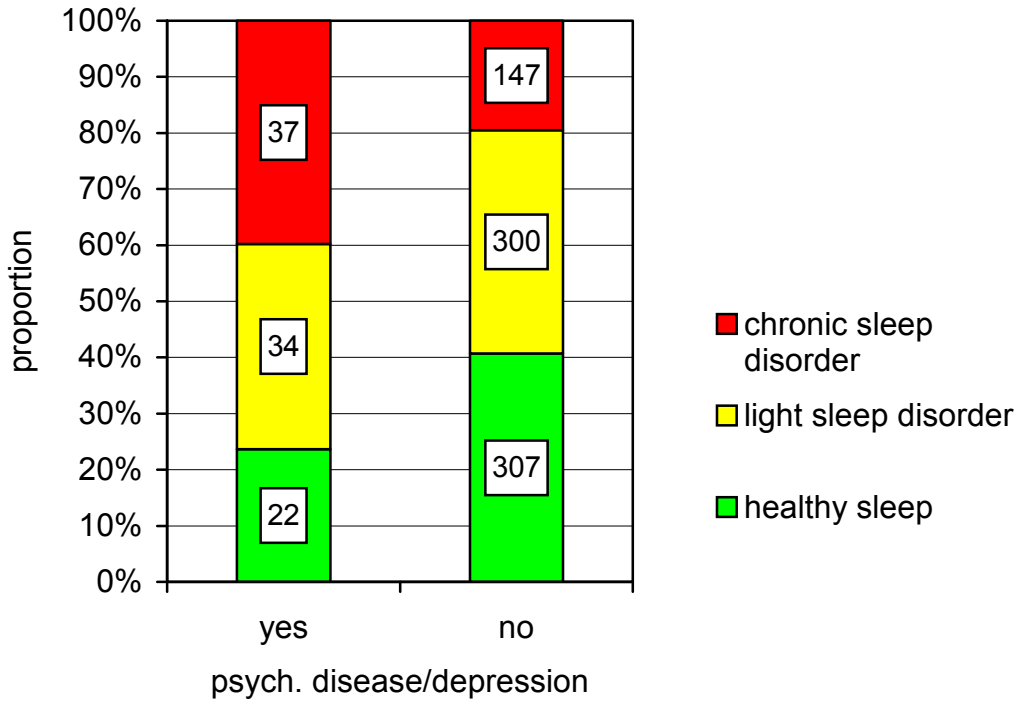


Fig. 84: Sleep disturbance and mental health problems or depression

Osteoarthritis: Here also, SLE patients with osteoarthritis were represented by much more poor sleepers than good sleepers (Fig.25).

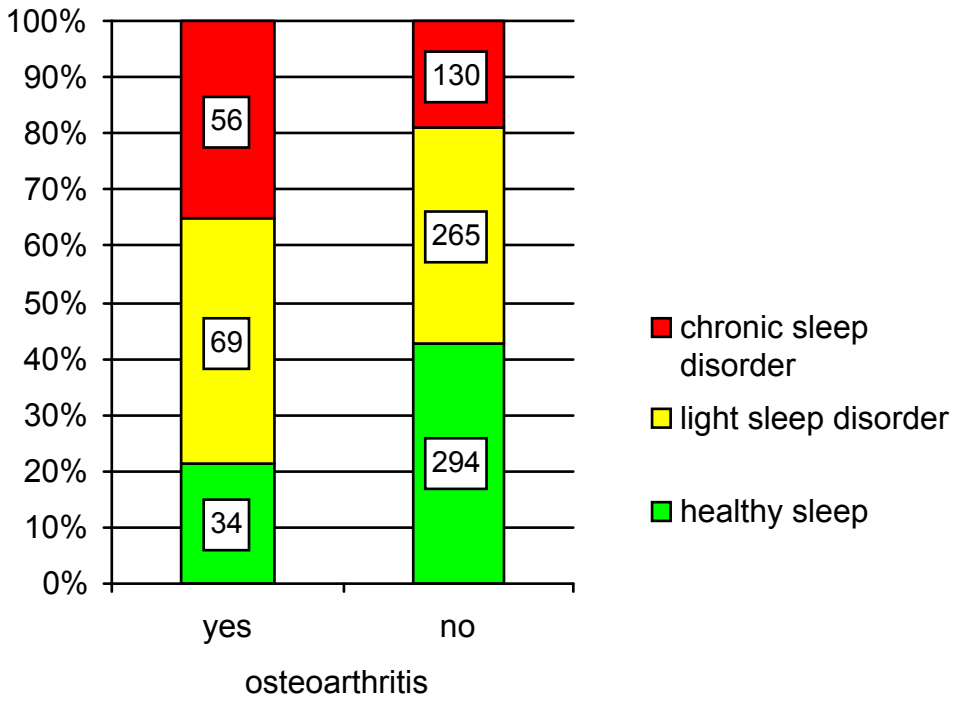


Fig.25: Sleep disturbance and osteoarthritis

Scarring skin disease: Here patients without this disease were obviously more often good sleepers than those having this complication (Fig.26).

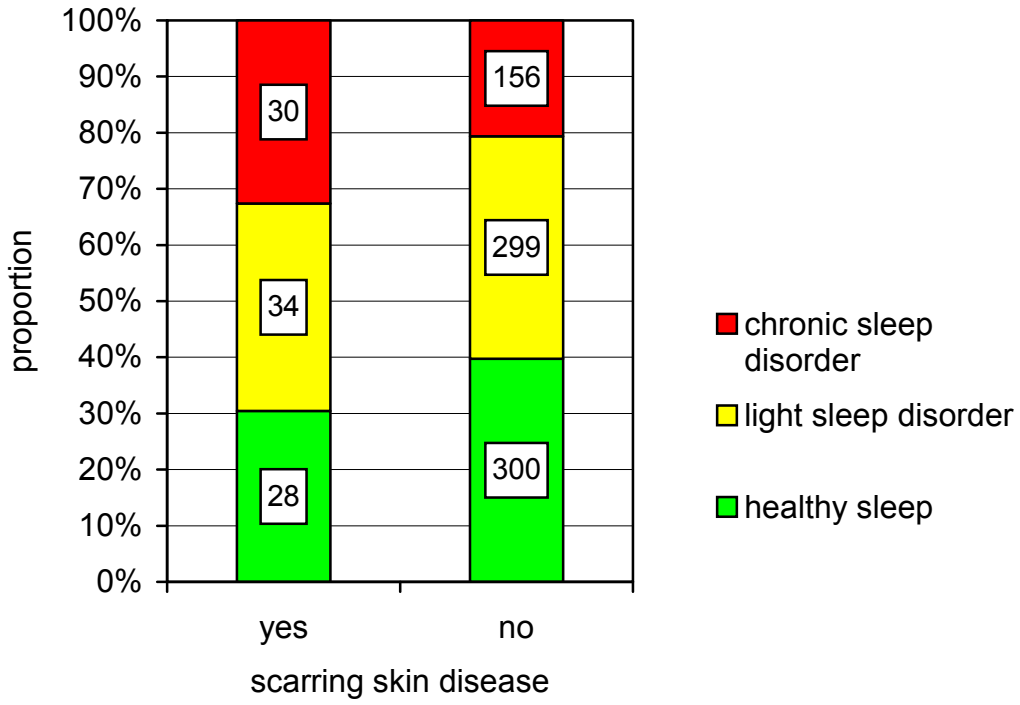


Fig. 26: Sleep disturbance and scarring skin disease

Osteoporosis: Nearly 40% of patients with osteoporosis were chronic poor sleepers whereas less than 30% were good sleepers (Fig.27).

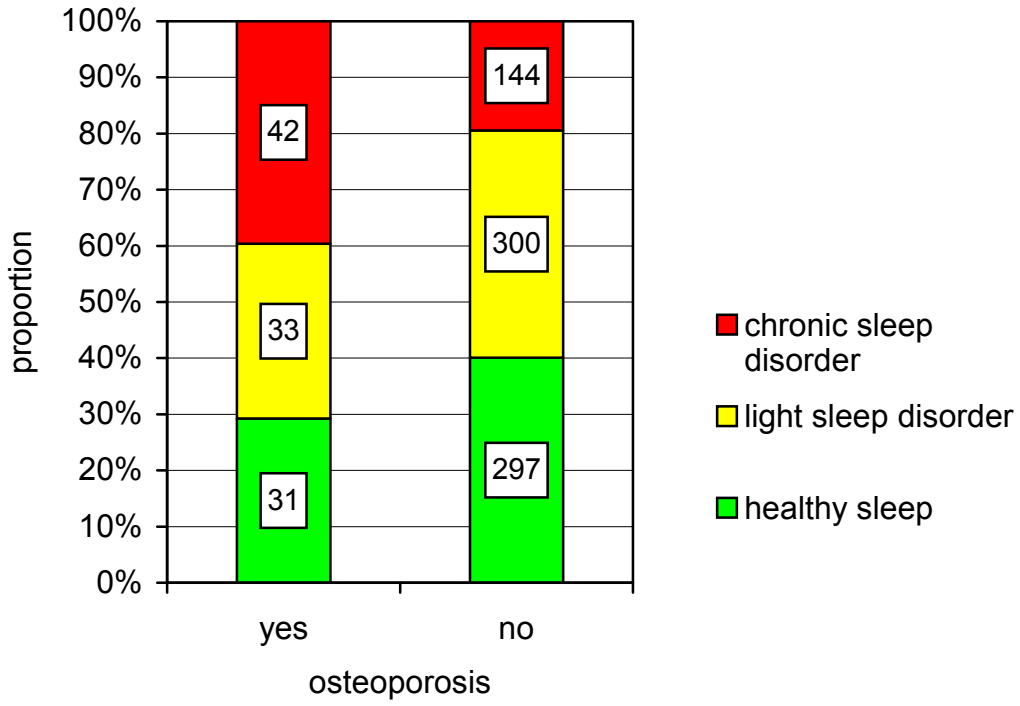


Fig. 97: Sleep disturbance and osteoporosis

Fibromyalgia: Less than 20% of the patients with fibromyalgia were good sleepers and more than 80% had some form of sleep disorder which was chronic in 39.6%.

<

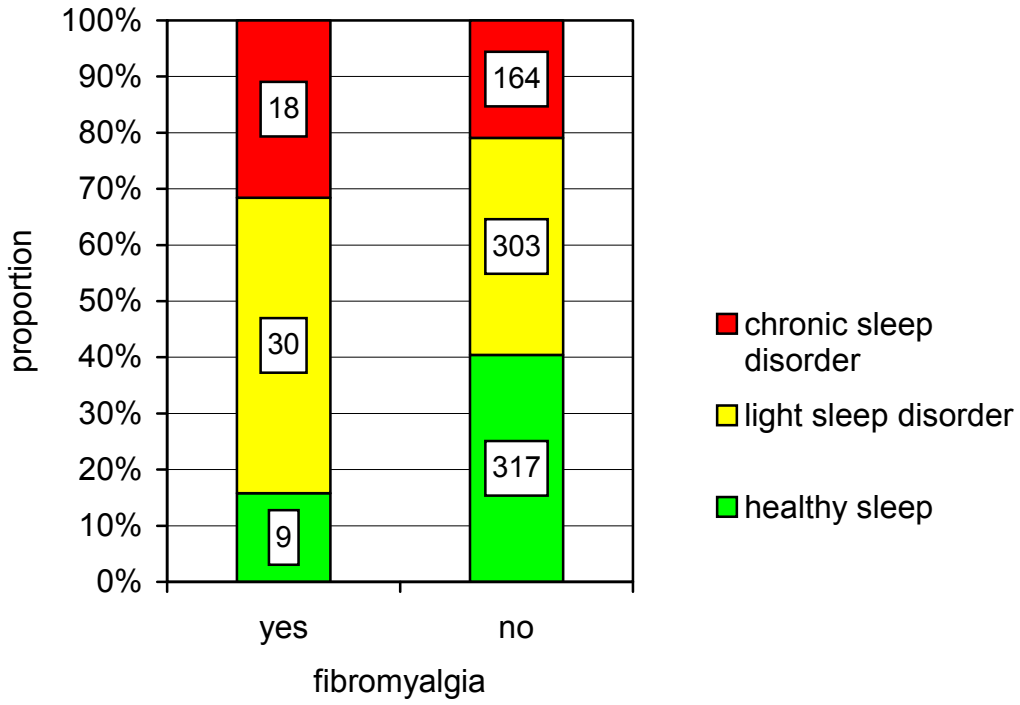


Fig. 18: Correlation of sleep disturbance with fibromyalgia

## 6.4 Statistical analysis of the results – multivariate analysis

Using the multivariate analysis, six variables were found to have a significant influence on the quality of sleep in SLE patients as measured by means of PSQI. The odds ratio estimates (Tab. 17) show that an age over 50, hypertension and, non smoking increase the risk of sleep disorders in SLE patients, while being occupied and in general good health as well as suffering from less than three restrictions of daily living reduce it.

The same variables were found to be correlated with a PSQI <5 and again a younger age, an occupation and normotension reduced the risk for sleep disorders. As for the other variables there were contradictory results: non smoking, a good general health and less than 3 restrictions increased the risk.

The risk for severe sleep disorders (PSQI >10) was statistically significant influenced by age, working status, general health, pain in the last 7 days, osteoporosis and the use of analgesics and psychotropic drugs. The presence of each of these factors increased the risk.

Tab. 17: Predictors of sleep quality: Odds ratios (95% confidence interval in parenthesis) for parameters which had been identified as influencing variables in multivariate analyis

| | PSQI total | PSQI > 5 | PSQI > 10 |
|---|---|---|---|
| Age<br>≤ 50 vs. >50 | 1.833<br>(1.281-2.624) | 1.775<br>(1.237-2.553) | 2.219<br>(1.440-3.455) |
| Working status<br>occupied vs. not occupied | 0.688<br>(0.479-0.989) | 0.663<br>(0.463-0.948) | 1.616<br>(1.016-2.581) |
| Hypertension<br>Yes vs. no | 1.866<br>(1.036-3.361) | 1.973<br>(1.114-3.623) | - |
| Smoking status<br>never vs. ever/ex | 1.650<br>(1.176-2.315) | 0.648<br>(0.463-0.905) | - |
| General Health<br>good vs. bad | 0.522<br>(0.333-0.820) | 2.519<br>(1.663-3.830) | 1.590<br>(1.030-2.455) |
| Restrictions of daily living<br>≤3 vs. >3 | 0.464<br>(0.294-0.732) | 2.872<br>(1.897-4.373) | - |
| Pain past 7 days<br>0-3 vs. >3 | - | - | 1.675<br>(1.062-2.651) |
| Osteoporosis<br>Yes vs. no | - | - | 2.067<br>(1.186-3.621) |
| Use of analgesics<br>Yes vs. no | - | - | 2.031<br>(1.304-3.168) |
| Use of psychopharmaceuti-cals<br>no vs. yes | - | - | 2.625<br>(1.561-4.447) |

# 7 DISCUSSION

Starting in the year 2001, with support of the Lupus Erythematodus Self Help Group, the LULA study was launched. This study is a long term prospective study over 10 years. It gathered medical and psychological information from Lupus patients in Germany. The aim of this observational study was to acquire in-depth information about SLE and to widen the spectrum of treatment options for the patients.

One of the major problems facing those patients is the chronic sleep disturbance and fatigue syndrome (Valencia-Flores et al. 1999; Tench et al. 2000; Gudbjornsson and Hetta 2001; Lashley 2003; Sweet et al. 2004; Costa et al. 2005; Moses et al. 2005; Iaboni et al. 2006; Greenwood et al. 2008). Therefore, we had the intention to further analyse the association between SLE and Sleep Disturbance. In this respect, the following questions needed to be answered:

- **Are sleep disorders common in patients with Systemic Lupus Erythematosus?**
- **Is there a correlation between Systemic Lupus Erythematosus and sleep disturbance?**
- **Which factors influence the sleep quality in patients with Systemic Lupus Erythematosus (age, certain medications, accompanying diseases)?**
- **Is there a correlation between sleep and perceived pain?**

## 7.1 Discussion of the methods

The patients involved in this study are members of the Self Help Group of Germany, ”Lupus Erythematodes Selbsthilfegemeinschaft”. They receive a membership magazine called “Schmetterling” every 3 months. This magazine informs about all what is new about the disease, research findings, treatment options, meetings, seminars, workshops, etc. With the assistance of this magazine, 1000 questionnaires were sent out to all the members to be filled out on a free basis. From the returned questionnaires, 851 were properly filled out and could be used for this study. This large number of filled-out

questionnaires expresses the great level of interest of the patients in the LuLa Study. It reflects the special interest of SLE-patients in sleep-related concerns, too, because in the year 2005 the questionnaire inclosed the PSQI (Pittsburgh Sleep quality index, Buysse et al.1989) for the evaluation of sleeping problems. Its validity and reliability were tested in patients with primary insomnia (Backhaus et al.2002), patients with psychiatric disorders (Buysse et al.1989, Doi et al.2000) and in case of various somatic diseases (Carpenter and Andrykowski 1998) as well as in geriatrics (Buysse et al 1991).

## 7.2 Discussion of the results

### 7.2.1 Disturbance in the quality of sleep in SLE patients in general

With the help of the questionnaire, it was found that 43% of our patients suffered from a poor or very poor quality of sleep. This high frequency of sleep disturbances confirms similar results of other studies dealing with sleep disorders in SLE patients (Valencia-Flores et al. 1999; Tench et al. 2000; Gudbjornsson and Hetta 2001; Lashley 2003; Costa et al. 2005; Moses et al. 2005; Iaboni et al. 2006; Greenwood et al. 2008).

In polysomnographic studies carried out on SLE patients with fatigue, it was found that they suffered significantly more from lighter sleep and had reduced duration and depth of sleep in phases 3 and 4 in comparison to their normal control counterparts. In addition, 77% of these patients showed a higher alpha-activity in the non-rem phase of sleep (Iaboni et al. 2006). In a similar study, Valencia-Flores et al. 1999 showed that SLE patients suffered from more sleep-associated respiratory disorders and disturbing sudden movements during sleep.

The reasons for these frequent sleep disturbances in Lupus patients still remain unclear. According to Lashley in 2003, many signs show that the immune system and sleep correlate somehow and that sleep disturbance may be an initiator of/ as well as a result from immune and auto-immune diseases.

Despite the fact that 43% of our patients described their sleep as “poor” or “very poor“, a sleeping efficiency of 80% with a mean of 6.8 hours of sleep was found, i.e. a fair amount of sleep. In order to find out the reasons for this contradiction we categorized the patients by means of the PSQI in three groups as proposed by Byusse et al. (1989, 1991): “Good sleepers” are patients with an undisturbed sleep (PSQI point >5), “moderate sleepers” are those who complain of slight or moderate sleep disturbance (PSQI points 6-10) and “poor sleepers” are patients with chronic and severe sleeping disorders (PSQI points >10). In this way, we were able to analyze factors such as age, comorbidities and medications used in order to find possible correlations and factors causing the sleep disturbance.

### 7.2.2 Correlation between sleep disturbance and the age of the patients

In this study, 49.1% of the patients were between 40 and 60 years old, 26.4% younger than 40 and 24.5% older than 60. This general older age of the patients indicates that the sleep disorders are rather a natural age-related problem than primarily related to SLE as a disease. The multivariate analysis showed a statistically significant correlation between ages of patients over 50 and sleep disturbance in general (Odds Ratio: 1,775; 95% confidence interval: 1.237-5.2553) and with severe sleeping problems (P< 0,0001; Odds Ratio: 2.219; 95% confidence interval: 1.440-3.455). The mean age of the patients with healthy sleep was 46 years, that with light sleeping disorder was 49 and that with severe chronic problems were 53 years (P< 0,0001).

It is generally known that sleep disturbance occurs quiet often in elderly patients (Monane 1992; Neubauer 1999; Rajput and Bromley 1999; Wilner 2004) and it is believed that half of the population over 65 years suffer from insomnia (Monane 1992) especially women (Vitiello et al. 2004). This may be partly related to the postmenopausal estrogen deficiency because sleep disorders frequently start in the postmenopausal period and their incidence increases with age (Moe 1999).

In our study, 49% of both sexes suffered from waking up “every night” or “often” which is evaluated to be more stressful than difficulty to fall asleep (Durrence et al. 2004) which has occurred in about a third of our patients.

A benign hypertrophy of the prostate in men and a weakening in the urethral sphincter in women cause patients to wake up to pass urine (Wolkove et al. 2007). According to Sutton et al. (2001) age alone is not a predictor for sleep disruption.

Similarly,in our study, waking up at night is not believed to be caused by the increasing age alone but age may be a background for the other factors and co-morbidities.

### 7.2.3 Correlation with the intake of certain medication

Our results showed that for nearly every medication used for the treatment of SLE, there was somehow a correlation with chronic sleep disturbance; a higher percentage of those patients taking a medication showed severe sleep disturbance in comparison to the patients who did not take these medicaments. On the other hand, those patients who had no sleep disorder were mainly patients not taking these medications and patients with light sleeping problems were almost equally represented by those taking and those not taking the medication. Using the multivariate analysis, we found out that neither general drug intake nor the use of specific medicaments increased the risk of sleep disorders in SLE patients, but with regard to the risk of developping a severe sleep disturbance, (PSQI) statistically significantly increased with the use of analgesics and psychopharmaceuticals.

By means of the univariate analysis, there was a strong correlation between patients taking non-steroidal antirheumatic medications (**NSAR**), and sleep disorder. From the patients taking NSAR, 32.7% suffered from severe sleep disorders and only 25.0% had a healthy sleep. From those who did not intake NSAR 43.1% had a healthy sleep and 18.5 % had very bad sleep. This correlation was found to be statistically significant ($P< 0,0001$).

In NSAR, there are a group of active ingredients that inhibit the cyclooxygenase enzyme (COX) which is partly involved in the synthesis of prostaglandine that in turn plays a role in both the development of pain and the regulation of sleep (Urade and Hayaishi 1999; Hayaishi 2002). This correlation could be clearly seen in animal tests: medically induced inhibition of COX-2 enzyme leading to statistically significant reduction of non-REM sleep in rats (Terao et al. 1998) and in rabbits (Yoshida et al. 2003).

As for the other **analgesics,** we could not find comparable molecular correlations in the literature. However, in our study, these analgesics provoked a nearly similar percentage of severe and light sleeping disorders as NSAR. In the studies described by Onen et al. (2005), the use of analgesics lead to a reduction of sleep efficiency, a higher incidence of waking up at night and non-REM sleep as well as a decreased slow-wave-sleep and REM-sleep without an explanation of a detailed cause for it.

Another situation exists with the use of **Steroids.** A clear correlation with sleep does not yet exist. In a study described by Costa et al. (2005), there was a correlation seen between the intake of prednisone and poor sleep whereas another study by Tench et al. (2000) showed the contrary. The reason behind this may lie in the dosage as for example when dexamethason is given in a high dosage, the slow-wave-sleep is inhibited while when it is given in small amounts the latter is induced (Vazquez-Palacios et al. 2001). The reaction of steroids on sleep EEG induces a higher cortisone level in the blood and an inhibition of cortisone releasing hormones which in turn increase slow-wave-sleep (Steiger 2002; Friess et al. 2004). Our study showed a correlation between intake of steroids and sleep disturbance: more than 30% of patients taking steroids more than 7.5mg had chronic sleep disorders while only 20% of the patients without steroids had that ($P< 0,05$). In the present investigation, the multivariate analysis verified a correlation between the use of psychopharmaca and severe sleep disorders with a PSQI over 10 (Odds Ratio: 2.625, 95% confidence interval: 1.561-4.447). A similar interrelationship was reported in other studies (Pearson et al. 2008; Tikkinen et al. 2009).

Similar correlations existed with other medications as for example those used for the treatment of osteoporosis, GIT disorders, dermal lesions, cardiac diseases and hyperten-

sion. Since the medications were numerous and varied widely, it would have been difficult to run an investigation for each medication used on the exact mechanism of action in relation to sleep disturbance. However, it is clearly seen that in general medications used by SLE patients increasingly cause sleep disturbance.

In this context, it is important to know, that the consumption of multiple drugs, which often is the case in SLE patients, may deteriorate the overall quality of sleep and especially each of the following components: subjective quality, latency of sleep, duration of sleep, extrinsic disturbances and consumption of sleeping draughts (Vazquez Garcia et al. 2000). This fact may induce a vicious circle: The presence of sleep disorders leads to the intake of further drugs which possibly aggravate the problem.

But the here observed correlation between the use of psychotropic drugs and sleep disorders may indicate a frequent occurence of psychiatric disorders in SLE patients which will be discussed later (see chapter 7.4).

## 7.3 Sleep disturbance and pain

In our study, the patients had to register their pain experience on a visual analogue scale. Patients with healthy sleep made registration on this scale of 2,0 ± 2,0 points while patients with slight sleep disturbance registered pain of 3,5 ± 2,5 points and those with severe sleep disorders 4,8±2,6 points. This difference between the 3 groups was statistically significant ($P < 0{,}001$). In the multivariate analysis, “pain perceived in the past 7 days” with an intensity of more than 3 points was shown to be a predictor of chronic sleeping problems (Odds Ratio: 1.675; 95% confidence interval: 1.062-2.651).

The correlation between sleep and pain is well examined in the literature. Gudbjornsson and Hetta in 2001 showed that even if SLE patients sleep longer, they often suffer from taking a long time till falling asleep and they frequently wake up through the night. They wake up in the morning not really refreshed and suffer more than healthy controls from a fatigue syndrome (Gudbjornsson and Hetta 2001). Jump et al. (2005) commented that pain is a stronger predictor for fatigue than the disease activity itself. Lam-

berg (1999) said that waking up at night or in the early morning is generally caused by pain. In a Canadian study, 44% of the patients suffering from pain had sleeping problems and that the more the pain, the worse is the sleeping disturbance or non-refreshing sleep (Sutton et al. 2001).

On the other hand, sleep disturbance itself may initiate pain (Moldofsky 2004; Davies et al. 2008): Some studies showed that a few nights without refreshing sleep for normal healthy individuals may result in non-specific generalized muscular pain and fatigue.

Another study was conducted on twelve healthy middle aged-women which were deprived on 3 consecutive nights from their slow wave sleep. Each time when the EEG discovered Delta waves, an 85 db loud sound occurred till the disappearance of the Delta waves. The slow wave sleep was reduced even if the total sleep duration and efficiency were only minimally affected. After the last day, the pain threshold of the tested women has decreased by 24% and they complained of fatigue, being unwell and loss of vitality (Lentz et al. 1999). In a similar study with 9 healthy men who were deprived from sleep for 40 hours, a hyperalgesic effect occurred. After slow wave sleep an analgetic effect was detected and it was considered to be more effective than the intake of Level 1 analgesics as prescribed by the WHO (Onen et al. 2001).

These results show that the sleep disturbance in SLE patients may influence much of the symptoms of the disease and that the treatment of sleep disturbance may be of general therapeutic value to the patients.

## 7.4 Correlation with comorbidities and other factors

In this study, by means of univariate analysis, statistically significant correlations were found with many associated diseases/co-morbidities of SLE. A higher percentage of patients with these diseases showed chronic sleep disturbance than those who did not have these diseases. This was seen with the following co-morbidities: hypertension, asthma, chronic liver disease, gastrointestinal or metabolic disorder, psychiatric diseases,arthritis, scarring tissue disease, osteoporosis and fibromyalgia. However, patients

with associated diabetes mellitus and tumor disease did not show any correlation with sleep disturbance. The multivariate analysis only detected an increased risk of sleep disorders in patients with a concomitant hypertension.

In recent clinical studies, no causal relationship has been found between sleep and **hypertension** (Phillips and Mannino 2007; Phillips et al. 2009). It seems questionable whether the correlation found in our study was of any clinical relevance because we only could affirm a correlation between the presence of hypertension and PSQI in general and slight sleep disturbances but not between severe sleep disorders and hypertension. Therefore, further investigations are recommended to clarify an assumed higher risk of sleep disorders in hypertensive SLE patients

For the other comorbidities which were found to influence sleep in univariate analysis, the published data are controverse.

As for **arthrosis, fibromyalgia and osteoporosis** the correlation may be related to pain. Especially with osteoporosis in men and women, it is generally accepted that it results in reduced activity and muscular pain (Rantanen et al. 1999; Avlund et al. 2003; Goldman et al. 2007; Dam et al. 2008). It is then expected that this may result in depression and reduction in the quality of life as well as sleep disturbance.

The correlation between sleep and **scarring tissue disease** is not always clear, too. There could be a correlation when combined with itching sensation that prevents from sleeping or that occurs more often at night (Patel, 2007 ).

As for patients with **chronic liver disease** they suffer frequently from sleep disruption. However, no causal relation could be tracked down to a certain lab parameter or to the basic disease thus it is considered to be a multifactorial phenomenon (Cauch-Dudek, 1998; Mostacci, 2008; Newton, 2008 ).

A clinically relevant problem is the relation between sleep disorder and **mental health problems/depression**: 39.8% of these patients suffered from chronic sleep disorder in comparison to 19.5% of the patients without psychiatric problems ($P < 0{,}001$). The in-

take of psychopharmacological medication was proved to be a predictor for chronic sleep disturbance (Odds Ratio: 2.625; confidence interval: 1.561-4.447).

The relation between sleep and depression is well known however both problems influence each other: An insomnia on one hand is accepted to be a predictor for depression (Breslau et al. 1996; Gutman and Nemeroff 2005). On the other hand in sleep diagnostic centers, it has been documented that 35% of sleep disorders are related to associating psychological problems (Coleman 1983; Buysse et al. 1989). Costa et al. (2005) observed sleep disturbance in 56% of their SLE patients. In their study, a "depressed mood" was the only independent determinant documented. Mc Kinley et al. in 1995 see in the coincidence of sleep disturbance occurring with depression in SLE patients a causal relationship with fatigue-syndrome. They suggest one of two paths: either SLE and sleep disturbance lead to fatigue over the depression path or SLE and depression lead to fatigue over the sleep path.

Beside the above discussed parameters, we found that **general health** (Odds Ratio: 1.616, 95% confidence interval: 1.016-2.581, P <0.0001) and **working status** (Odds Ratio: 1.590, 95% confidence interval: 1.030-2.455, P <0.0001) are correlated with a severe sleep disorder expressed by a PSQI >10. The interrelationship to general health status is easy to understand because it is a well-proven fact that sleep quality is influenced by a variety of stress impacts caused by intrinsic and extrinsic factors and that a bad general health is an independent risk factor for reduced quality of life and sleep disorders (Buysse et al. 1989; Monane 1992; Dobkin et al. 1998; Neubauer 1999; Paunio et al. 2009; Yoshimura et al. 2009). This fact is valid not only for SLE patients but for everybody.

The correlation of working status and sleep disorders has not yet been described in SLE patients. On the one side, being physically able to work may be interpreted as a sign of a less advanced stage of disease with less severe symptoms, among them chronic sleep disorders. On the other side, in general, the impossibility to work may have a negative impact on the social and emotional well-being and mental health (Etches et al. 2006; Baune et al. 2008; Baune et al. 2009).

## 7.5 Conclusion and suggestion for further studies

The above study shows that sleep disturbance plays an important role in SLE patients. However, the exact cause should be considered to be multi-factorial and therefore sleep disorders in this group of patients may be difficult to treat. Pain, comorbidities and medications used could cause sleep disturbance but this latter may also influence the disease manifestations. Nevertheless, an improvement in sleep quality and quantity may break this vicious circle and lead to an improvement in the general health of the patients and to a better quality of life (Onen et al. 2005).

The role played by sleep disruption in SLE patients was underestimated till this time. In an Australian study (Moses et al. 2005) 70% of the questioned SLE patients did not get enough help for their sleeping problem.

Mc Kinley et al. (1995) commented that chronic sleep disturbance in SLE patients together with depressive moods lead to a fatigue syndrome. Further studies on the correlations between sleep, depression and fatigue would be very useful since many of the SLE patients are very restricted in their ability to work and social relations as well as in their general quality of life.

# 8 Abstract

This investigation was conducted in the context of the “Lula Study” which was started in 2001 and is running for a period of 10 years. It aims to get new insight in Systemic Lupus Erythematosus (SLE) in order to optimize the treatment.

In 2005, we analysed sleep disorders in members of a German SLE self help organization. A questionnaire containing the Pittsburg Sleep Quality Index (PSQI) was filled out by 851 SLE patients (94% women, 6% men, mean age: 48.7 ± 13.8 years) and the data was statistically analysed.

In general, 57.9% of our patients reported to sleep very or fairly good and 80% stated never to take sleeping pills. The mean PSQI of all patients was 7.35 out of 19 possible points. By categorizing the PSQI values, we found out that only 38.7% of the patients had a quiet sleep (PSQI 0-5), 39.4% slight sleeping problems (PSQI 6-10) and 22.0% severs sleep disorders (PSQI >10).

Univariate analysis of data showed that age, pain, medication (NSAR, analgesics, steroids >7.5mg, psychopharmaca as well as a drug therapy of osteoporosis, hypertension/cardiac problems, gastrointestinal and metabolic disorders) in addition to comorbidities (hypertension, asthma/breathing problems, hepatic/gastrointestinal, metabolic disorders, psychological diseases/depression, arthrosis, scarring skin disease, osteoporosis, fibromyalgie) were correlated with the incidence of sleep disorders. By multivariate analysis, we found out that the incidence of severe sleep disorders (PSQI) was correlated with age, working state, general health, pain, osteoporosis and psychotropic drugs. The results were discussed in the context of literature.

As conclusion, sleep disorders in SLE patients are of multifactorial origin. There are numerous interactions of the underlying and comorbid disorders and therefore the treatment must be based on a multidisciplinary approach which accounts for the patient’s individual needs.

# 9 References


1. ABU-SHAKRA, M., SHOENFELD, Y. (2001): Azathioprine therapy for patients with systemic lupus erythematosus. Lupus 10, 152-153.

2. ADAMS, S. G., JR., DAMMERS, P. M., SAIA, T. L., BRANTLEY, P. J., GAYDOS, G. R. (1994): Stress, depression, and anxiety predict average symptom severity and daily symptom fluctuation in systemic lupus erythematosus. J Behav Med 17, 459-477.

3. ADU, D., CROSS, J., JAYNE, D. R. (2001): Treatment of systemic lupus erythematosus with mycophenolate mofetil. Lupus 10, 203-208.

4. AHMED, A. R., HOMBAL, S. M. (1984): Cyclophosphamide (Cytoxan). A review on relevant pharmacology and clinical uses. J Am Acad Dermatol 11, 1115-1126.

5. ASPLUND, R. (1999): Sleep disorders in the elderly. Drugs Aging 14, 91-103.

6. AVLUND, K., VASS, M., HENDRIKSEN, C. (2003): Onset of mobility disability among community-dwelling old men and women. The role of tiredness in daily activities. Age Ageing 32, 579-584.

7. BACKHAUS, J., JUNGHANNS, K., BROOCKS, A., RIEMANN, D., HOHAGEN, F. (2002): Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. J Psychosom Res 53, 737-740.

8. BAE, S. C., HASHIMOTO, H., KARLSON, E. W., LIANG, M. H., DALTROY, L. H. (2001): Variable effects of social support by race, economic status, and disease activity in systemic lupus erythematosus. J Rheumatol 28, 1245-1251.

9. BALOW, J. E. (1990): Treatment and monitoring of patients with lupus nephritis. Nephrol Dial Transplant 5 Suppl 1, 58-59.

10. BARGMAN, J. M. (2009): How did cyclophosphamide become the drug of choice for lupus nephritis? Nephrol Dial Transplant 24, 381-384.

11. BAUNE, B. T., CANIATO, R. N., AROLT, V., BERGER, K. (2009): The effects of dysthymic disorder on health-related quality of life and disability days in persons with comorbid medical conditions in the general population. Psychother Psychosom 78, 161-6.

12. BAUNE, B. T., CANIATO, R. N., GARCIA-ALCARAZ, M. A., BERGER, K. (2008): Combined effects of major depression, pain and somatic disorders on general functioning in the general adult population. Pain 138, 310-7.

13. BECK, S. L., SCHWARTZ, A. L., TOWSLEY, G., DUDLEY, W., BARSEVICK, A. (2004): Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients. J Pain Symptom Manage 27, 140-148.

14. BOMBARDIER, C., GLADMAN, D. D., UROWITZ, M. B., CARON, D., CHANG, C. H. (1992): Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 35, 630-640.

15. BORBA, E. F., BONFA, E. (2001): Longterm beneficial effect of chloroquine diphosphate on lipoprotein profile in lupus patients with and without steroid therapy. J Rheumatol 28, 780-785.

16. BRESLAU, N., ROTH, T., ROSENTHAL, L., ANDRESKI, P. (1996): Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 39, 411-418.

17. BREY, R. L., PETRI, M. A. (2003): Neuropsychiatric systemic lupus erythematosus: miles to go before we sleep. Neurology 61, 9-10.

18. BUYSSE, D. J., REYNOLDS, C. F., 3RD, MONK, T. H., BERMAN, S. R., KUPFER, D. J. (1989): The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28, 193-213.

19. BUYSSE, D. J., REYNOLDS, C. F., 3RD, MONK, T. H., HOCH, C. C., YEAGER, A. L., KUPFER, D. J. (1991): Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). Sleep 14, 331-338.

20. COLE, J. C., MOTIVALA, S. J., BUYSSE, D. J., OXMAN, M. N., LEVIN, M. J., IRWIN, M. R. (2006): Validation of a 3-factor scoring model for the Pittsburgh sleep quality index in older adults. Sleep 29, 112-6.

21. COLEMAN, R. M. (1983): Diagnosis, treatment, and follow-up of about 8,000 sleep/wake disorder patients. Zit. n. Buysse et al. (1988).

22. COOK, R. J., GLADMAN, D. D., PERICAK, D., UROWITZ, M. B. (2000): Prediction of short term mortality in systemic lupus erythematosus with time dependent measures of disease activity. J Rheumatol 27, 1892-1895.

23. CORZILLIUS, M., SCHROEDER, J. O., EULER, H. H. (1991): [Comparison of three indices for the evaluation of disease activity in systemic lupus erythematosus]. Z Rheumatol 50, 371-377.

24. COSTA, D. D., BERNATSKY, S., DRITSA, M., CLARKE, A. E., DASGUPTA, K., KESHANI, A., PINEAU, C. (2005): Determinants of sleep quality in women with systemic lupus erythematosus. Arthritis Rheum 53, 272-278.

25. DAM, T. T., EWING, S., ANCOLI-ISRAEL, S., ENSRUD, K., REDLINE, S., STONE, K. (2008): Association between sleep and physical function in older men: the osteoporotic fractures in men sleep study. J Am Geriatr Soc 56, 1665-1673.

26. DAVIES, K. A., MACFARLANE, G. J., NICHOLL, B. I., DICKENS, C., MORRISS, R., RAY, D., MCBETH, J. (2008): Restorative sleep predicts the resolution of chronic widespread pain: results from the EPIFUND study. Rheumatology (Oxford) 47, 1809-1813.

27. DE VITA, S., NERI, R., BOMBARDIERI, S. (1991): Cyclophosphamide pulses in the treatment of rheumatic diseases: an update. Clin Exp Rheumatol 9, 179-193.

28. DOBKIN, P. L., DA COSTA, D., FORTIN, P. R., EDWORTHY, S., BARR, S., ESDAILE, J. M., SENECAL, J. L., GOULET, J. R., CHOQUETTE, D., RICH, E., BEAULIEU, A., CIVIDINO, A., ENSWORTH, S., SMITH, D., ZUMMER, M., GLADMAN, D., CLARKE, A. E. (2001): Living with lupus: a prospective pan-Canadian study. J Rheumatol 28, 2442-2448.

29. DOBKIN, P. L., FORTIN, P. R., JOSEPH, L., ESDAILE, J. M., DANOFF, D. S., CLARKE, A. E. (1998): Psychosocial contributors to mental and physical health in patients with systemic lupus erythematosus. Arthritis Care Res 11, 23-31.

30. DURRENCE, H. H., ROTH, T., KRYSTAL, A. D., WESSEL, T., SCHAEFER, K. (2004): Twelve-month efficacy and safety assessment of eczopiclone in patients with chronic insomnia. CME syllabus and proceedings summary of the American Psychiatric Association 56th Institute on Psychiatric Services: October 6-10, 2004; Atlanta, Georgia. Poster 28.

31. ETCHES, V., FRANK, J., DI RUGGIERO, E., MANUEL, D. (2006): Measuring population health: a review of indicators. Annu Rev Public Health 27, 29-55.

32. FISCHER-BETZ, R., WESSEL, E., RICHTER, J., WINKLER-ROHLFING, B., WILLERS, R., SCHNEIDER, M. (2005): [Lupus in Germany: analysis within the German lupus self-help organization (LULA)]. Z Rheumatol 64, 111-122.

33. FOX, D. A., MCCUNE, W. J. (1994): Immunosuppressive drug therapy of systemic lupus erythematosus. Rheum Dis Clin North Am 20, 265-299.

34. FRIESS, E., TAGAYA, H., GRETHE, C., TRACHSEL, L., HOLSBOER, F. (2004): Acute cortisol administration promotes sleep intensity in man. Neuropsychopharmacology 29, 598-604.

35. GINZLER, E. M., ARANOW, C. (2005): Mycophenolate mofetil in lupus nephritis. Lupus 14, 59-64.

36. GOLDMAN, S. E., STONE, K. L., ANCOLI-ISRAEL, S., BLACKWELL, T., EWING, S. K., BOUDREAU, R., CAULEY, J. A., HALL, M., MATTHEWS, K. A., NEWMAN, A. B. (2007): Poor sleep is associated with poorer physical performance and greater functional limitations in older women. Sleep 30, 1317-1324.

37. GREENWOOD, K. M., LEDERMAN, L., LINDNER, H. D. (2008): Self-reported sleep in systemic lupus erythematosus. Clin Rheumatol 27, 1147-1151.

38. GUDBJORNSSON, B., HETTA, J. (2001): Sleep disturbances in patients with systemic lupus erythematosus: a questionnaire-based study. Clin Exp Rheumatol 19, 509-514.

39. GUTMAN, D. A., NEMEROFF, C. B. (2005): Insomnia and depression. Medscape Primary Care 7 (1), 2005, Article 498024.

40. HAY, E. M., BACON, P. A., GORDON, C., ISENBERG, D. A., MADDISON, P., SNAITH, M. L., SYMMONS, D. P., VINER, N., ZOMA, A. (1993): The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Q J Med 86, 447-458.

41. HAYAISHI, O. (2002): Molecular genetic studies on sleep-wake regulation, with special emphasis on the prostaglandin D2 system. J Appl Physiol 92, 863-868.

42. HOUSSIAU, F. A., GINZLER, E. M. (2008): Current treatment of lupus nephritis. Lupus 17, 426-430.

43. IABONI, A., IBANEZ, D., GLADMAN, D. D., UROWITZ, M. B., MOLDOFSKY, H. (2006): Fatigue in systemic lupus erythematosus: contributions of disordered sleep, sleepiness, and depression. J Rheumatol 33, 2453-2457.

44. ISENBERG, D. A., GORDON, C. (2000): From BILAG to BLIPS--disease activity assessment in lupus past, present and future. Lupus 9, 651-654.

45. JIMENEZ, S., CERVERA, R., FONT, J., INGELMO, M. (2003): The epidemiology of systemic lupus erythematosus. Clin Rev Allergy Immunol 25, 3-12.

46. JONES, R. B., WALSH, M., SMITH, K. G. (2009): What is the value of mycophenolate mofetil as induction and maintenance therapy in lupus nephritis? Curr Opin Rheumatol 21, 256-261.

47. JUMP, R. L., ROBINSON, M. E., ARMSTRONG, A. E., BARNES, E. V., KILBOURN, K. M., RICHARDS, H. B. (2005): Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support. J Rheumatol 32, 1699-1705.

48. KAHN, M. F. (1990): The treatment of lupus in the 1990s. Clin Exp Rheumatol 8 Suppl 5, 45-49.

49. KARLSON, E. W., DALTROY, L. H., RIVEST, C., RAMSEY-GOLDMAN, R., WRIGHT, E. A., PARTRIDGE, A. J., LIANG, M. H., FORTIN, P. R. (2003): Validation of a Systemic Lupus Activity Questionnaire (SLAQ) for population studies. Lupus 12, 280-286.

50. LASH, A. A. (1998): Quality of life in systemic lupus erythematosus. Appl Nurs Res 11, 130-137.

51. LASHLEY, F. R. (2003): A review of sleep in selected immune and autoimmune disorders. Holist Nurs Pract 17, 65-80.

52. LENTZ, M. J., LANDIS, C. A., ROTHERMEL, J., SHAVER, J. L. (1999): Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. J Rheumatol 26, 1586-1592.

53. LIANG, M. H., SOCHER, S. A., LARSON, M. G., SCHUR, P. H. (1989): Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum 32, 1107-1118.

54. MCCUNE, W. J., FOX, D. (1989): Intravenous cyclophosphamide therapy of severe SLE. Rheum Dis Clin North Am 15, 455-477.

55. MCKINLEY, P. S., OUELETTE, S. C., WINKEL, G. H. (1995): The contributions of disease activity, sleep patterns, and depression to fatigue in systemic lupus erythematosus. Arthritis Rheumatism 38, 826-834.

56. MEINAO, I. M., SATO, E. I., ANDRADE, L. E., FERRAZ, M. B., ATRA, E. (1996): Controlled trial with chloroquine diphosphate in systemic lupus erythematosus. Lupus 5, 237-241.

57. MIESCHER, P. A., BERIS, P. (1984): Immunosuppressive therapy in the treatment of autoimmune diseases. Springer Semin Immunopathol 7, 69-90.

58. MOE, K. E. (1999): Reproductive hormones, aging, and sleep. Semin Reprod Endocrinol 17, 339-48.

59. MOLDOFSKY, H. (2004): Pain and insomnia: What every clinician should know. Medscape Neurology & Neurosurgery 6 (2), 2004, Article 494872.

60. MOLDOFSKY, H., SCARISBRICK, P., ENGLAND, R., SMYTHE, H. (1975): Musculosketal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. Psychosom Med 37, 341-351.

61. MONANE, M. (1992): Insomnia in the elderly. J Clin Psychiatry 53, 23-28.

62. MOORE, R. A., DERRY, S. (2006): Systematic review and meta-analysis of randomised trials and cohort studies of mycophenolate mofetil in lupus nephritis. Arthritis Res Ther 8, R182.

63. MOSCA, M., BENCIVELLI, W., VITALI, C., CARRAI, P., NERI, R., BOMBARDIERI, S. (2000): The validity of the ECLAM index for the retrospective evaluation of disease activity in systemic lupus erythematosus. Lupus 9, 445-450.

64. MOSES, N., WIGGERS, J., NICHOLAS, C., COCKBURN, J. (2005): Prevalence and correlates of perceived unmet needs of people with systemic lupus erythematosus. Patient Educ Couns 57, 30-38.

65. NEUBAUER, D. N. (1999): Sleep problems in the elderly. Am Fam Physician 59, 2551-2560.

66. NIAMS. (2009): Handout on Health: Systemic Lupus Erythematosus. National Institute of Arthritis and Musculosceletal and Skin Diseases (NIAMS), http://www.niams.nih.gov/Health_Info/Lupus/default.asp [April 2009].

67. ONEN, S. H., ALLOUI, A., GROSS, A., ESCHALLIER, A., DUBRAY, C. (2001): The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. J Sleep Res 10, 35-42.

68. ONEN, S. H., ONEN, F., COURPRON, P., DUBRAY, C. (2005): How pain and analgesics disturb sleep. Clin J Pain 21, 422-431.

69. PARKE, A. L. (1988): Antimalarial drugs, systemic lupus erythematosus and pregnancy. J Rheumatol 15, 607-610.

70. PAUNIO, T., KORHONEN, T., HUBLIN, C., PARTINEN, M., KIVIMAKI, M., KOSKENVUO, M., KAPRIO, J. (2009): Longitudinal study on poor sleep and life dissatisfaction in a nationwide cohort of twins. Am J Epidemiol 169, 206-13.

71. PEARSON, V. E., GAMALDO, C. E., ALLEN, R. P., LESAGE, S., HENING, W. A., EARLEY, C. J. (2008): Medication use in patients with restless legs syndrome compared with a control population. Eur J Neurol 15, 16-21.

72. PHILLIPS, B., BUZKOVA, P., ENRIGHT, P. (2009): Insomnia did not predict incident hypertension in older adults in the cardiovascular health study. Sleep 32, 65-72.

73. PHILLIPS, B., MANNINO, D. M. (2007): Do insomnia complaints cause hypertension or cardiovascular disease? J Clin Sleep Med 3, 489-494.

74. RAJPUT, V., BROMLEY, S. M. (1999): Chronic insomnia: a practical review. Am Fam Physician 60, 1431-1442.

75. RANTANEN, T., GURALNIK, J. M., SAKARI-RANTALA, R., LEVEILLE, S., SIMONSICK, E. M., LING, S., FRIED, L. P. (1999): Disability, physical activity, and muscle strength in older women: the Women's Health and Aging Study. Arch Phys Med Rehabil 80, 130-135.

76. REDEKER, N., TAMBURRI, L., HOWLAND, C. (1998): Prehospital correlates of sleep in patients hospitalized with cardiac disease. Res Nurs Health 21, 27-37.

77. ROBERTS, W. N. (1997): Keys to managing systemic lupus erythematosus. Hosp Pract (Minneap) 32, 113-126.

78. SATO, E. I. (2001): Methotrexate therapy in systemic lupus erythematosus. Lupus 10, 162-164.

79. SNYDER-HALPERN, R., VERRAN, J. A. (1987): Instrumentation to describe subjective sleep characteristics in healthy subjects. Res Nurs Health 10, 155-63.

80. STEIGER, A. (2002): Sleep and the hypothalamo-pituitary-adrenocortical system. Sleep Med Rev 6, 125-138.

81. SUTTON, D. A., MOLDOFSKY, H., BADLEY, E. M. (2001): Insomnia and health problems in Canadians. Sleep 24, 665-670.

82. SWEET, J. J., DONINGER, N. A., ZEE, P. C., WAGNER, L. I. (2004): Factors influencing cognitive function, sleep, and quality of life in individuals with systemic lupus erythematosus: a review of the literature. Clin Neuropsychol 18, 132-147.

83. TENCH, C. M., MCCURDIE, I., WHITE, P. D., D'CRUZ, D. P. (2000): The prevalence and associations of fatigue in systemic lupus erythematosus. Rheumatology (Oxford) 39, 1249-1254.

84. TERAO, A., MATSUMURA, H., YONEDA, H., SAITO, M. (1998): Enhancement of slow-wave sleep by tumor necrosis factor alpha is mediated by cyclooxygenase-2 in rats. Neuroreport 2, 3791-3796.

85. TIKKINEN, K. A., AUVINEN, A., JOHNSON, T. M., 2ND, WEISS, J. P., KERANEN, T., TIITINEN, A., POLO, O., PARTINEN, M., TAMMELA, T. L. (2009): A systematic evaluation of factors associated with nocturia - the population-based FINNO study. Am J Epidemiol 170, 361-8.

86. TRANMER, J. E., MINARD, J., FOX, L. A., REBELO, L. (2003): The sleep experience of medical and surgical patients. Clin Nurs Res 12, 159-173.

87. URADE, Y., HAYAISHI, O. (1999): Prostaglandin D2 and sleep regulation. Biochim Biophys Acta 1436, 606-615.

88. UROWITZ, M. B., GLADMAN, D. D. (1999): Evolving spectrum of mortality and morbidity in SLE. Lupus 8, 253-255.

89. VALENCIA-FLORES, M., RESENDIZ, M., CASTANO, V. A., SANTIAGO, V., CAMPOS, R. M., SANDINO, S., VALENCIA, X., ALCOCER, J., RAMOS, G. G., BLIWISE, D. L. (1999): Objective and subjective sleep disturbances in patients with systemic lupus erythematosus. Arthritis Rheum 42, 2189-2193.

90. VAZQUEZ GARCIA, V. M., MACIAS FERNANDEZ, J. A., ALONSO DEL TESO, F., GONZALEZ LAS HERAS, R. M., DE TERESA ROMERO, G., ALVAREZ HURTADO, A. A., CARRETERO ARES, J. I. (2000): [The quality of sleep associated with polypharmacy]. Aten Primaria 26, 697-9.

91. VAZQUEZ-PALACIOS, G., RETANA-MARQUEZ, S., BONILLA-JAIME, H., VELAZQUEZ-MOCTEZUMA, J. (2001): Further definition of the effect of corticosterone on the sleep-wake pattern in the male rat. Pharmacol Biochem Behav 70, 305-310.

92. VENABLES, P. J. (1993): Diagnosis and treatment of systemic lupus erythematosus. Bmj 307, 663-666.

93. VITIELLO, M. V., LARSEN, L. H., MOE, K. E. (2004): Age-related sleep change: gender and estrogen effects on the subjective-objective quality relationships of healthy, noncomplaining older men and women. J Psychosom Res 56, 503-510.

94. WHO. (1986): Cancer Pain Relief. World Health Organization, Geneva.

95. WILNER, A. N. (2004): Conference Report - Highlights of the American Psychiatric Association 56th Institute on Psychiatric Services. . Current Perspectives Insomnia 4 [http://cme.medscape.com/viewarticle/495341] 03-01-2009.

96. WOLKOVE, N., ELKHOLY, O., BALTZAN, M., PALAYEW, M. (2007): Sleep and aging: 1. Sleep disorders commonly found in older people. CMAJ 176, 1299-1304.

97. YOSHIDA, H., KUBOTA, T., KRUEGER, J. M. (2003): A cyclooxygenase-2 inhibitor attenuates spontaneous and TNF-alpha-induced non-rapid eye movement sleep in rabbits. Am J Physiol Regul Integr Comp Physiol 285, R99-R109.

98. YOSHIMURA, K., OKA, Y., KAMOTO, T., TSUKAMOTO, T., OSHIRO, K., SUZUKAMO, Y., KINUKAWA, N., OGAWA, O. (2009): Night-time frequency, sleep disturbance and general health-related quality of life: is there a relation? Int J Urol 16, 96-100.

99. ZHU, B., CHEN, N., LIN, Y., REN, H., ZHANG, W., WANG, W., PAN, X., YU, H. (2007): Mycophenolate mofetil in induction and maintenance therapy of severe lupus nephritis: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant 22, 1933-1942.

100. ZINK, A., FISCHER-BETZ, R., THIELE, K., LISTING, J., HUSCHER, D., GROMNICA-IHLE, E., SPECKER, C., SCHNEIDER, M. (2004): Health care and burden of illness in systemic lupus erythematosus compared to rheumatoid arthritis: results from the National Database of the German Collaborative Arthritis Centres. Lupus 13, 529-536.

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# 11 Curriculum

| | |
|---|---|
| Name | Mariam Asfour |
| Date/place of birth | 18.08.1966 in Alexandria/Egypt |
| Family status | Married, two daughters |

**Education**

| | |
|---|---|
| 09/1970 - 06/1984 | Sainte Jeanne Antide, French school in Alexandria/Egypt |
| 09/1984 - 06/1989 | Studies of dentistry, Faculty of Dentistry, University Alexandria/Egypt. BDS in dental surgery. |
| 09/1992 - 09/1994 | Course of pediatric dentistry, King's College, University London/England.<br>Certified MSc of pediatric dentistry |

**Professional life**

| | |
|---|---|
| 11.1989 - 10.1990 | Clinical internship, University of Alexandria/Egypt |
| 11.1990 - 05.1991 | Dentist in Alexandria/Egypt (public service and private practice) |
| 10. 1992 - 09.1995 | Pediatric dentist, King's College Hospital, London/England |
| 02. 1996 - 06. 1999 | (Pediatric) dentist, private clinic in Djiddah/Saudi Arabia |
| 06.1999 - 01.2000 | Reorientation phase |
| 02.2000 - 03.2002 | Assistant dentist, P. Lüttgen, Neuss/Germany |
| 03.2002 - 06.2002 | Verification of equivalency, German licence to practice dentistry |
| 07.2002 - 07. 2005 | Dentist in a group practice in Düsseldorf/Germany |
| 08.2005 - 11.2005 | Preparation of my own practice |
| Since 12.2005 | Dentist in my own practice specialised in the treatment of children and anxious patients. |

# 12 Appendix

## 12.1 LuLa-Questionnaire

**Results of Chi-square tests**

Tab. 18: Results of Chi-square tests

| Parameter | Chi-square | Degree of freedom | Chi-square P |
|---|---|---|---|
| Sex | 2.6699 | 2 | 0.26317 |
| Occupation | 45.3730 | 10 | 0.00000 |
| Hypertension | 24.7857 | 2 | 0.00000 |
| Renal disorder | 3.5618 | 2 | 0.16849 |
| Diabetes mellitus | 12.0933 | 2 | 0.00237 |
| Tumour | 8.9237 | 2 | 0.01154 |
| Asthma | 6.2537 | 2 | 0.04385 |
| Hepatic disorder | 14.8204 | 2 | 0.00061 |
| Gastrointestinal disorder | 16.5646 | 2 | 0.00025 |
| Lipid metabolism disorder | 16.0964 | 2 | 0.00032 |
| Psychiatric disorder | 22.1098 | 2 | 0.00002 |
| Arthrosis | 31.6823 | 2 | 0.00000 |
| Dermal disorder | 7.3074 | 2 | 0.02589 |
| Osteoporosis | 22.0885 | 2 | 0.00002 |
| Fibromyalgia | 13.7400 | 2 | 0.00104 |
| Thrombosis | 4.2625 | 2 | 0.11869 |
| Abortion | 2.4073 | 2 | 0.30010 |
| Menopause | 18.8161 | 2 | 0.00008 |
| NSAR | 28.2845 | 2 | 0.00000 |
| Steroids < 7.5mg | 0.4119 | 2 | 0.81386 |
| Steroids > 7.5mg | 7.3268 | 2 | 0.02565 |
| Hydroxychloroquine | 2.2390 | 2 | 0.32644 |
| Azathioprine | 2.5811 | 2 | 0.27512 |
| Metothrexat | 3.8762 | 2 | 0.14398 |
| Cyclosporin A | 1.2175 | 2 | 0.54403 |
| Med. Osteoporosis | 13.7436 | 2 | 0.00104 |
| Med. Blood pressure/cardiac | 22.4721 | 2 | 0.00001 |
| Med. Analgesics | 53.1521 | 2 | 0.00000 |
| Med. hormones | 0.4783 | 2 | 0.78731 |
| Med. Cholestasis | 2.2872 | 2 | 0.31866 |
| Med. Psychopharmca | 41.9946 | 2 | 0.00000 |
| Med. Gastrointestinal | 32.2090 | 2 | 0.00000 |
| Med. Dermal | 12.0529 | 2 | 0.00241 |