



What are the determinants

And how can we optimize the management of

Fatigue in systemic lupus

An evidence-based update in 2021

Pr. Laurent ARNAUD

Department of Rheumatology

National Reference Center for Systemic Autoimmune Diseases, Strasbourg, France

Twitter: [Lupusreference](#)

What is **fatigue** ?

- ✓ **Nearly everyone** from the general population has experienced fatigue
- ✓ Yet, there is **not consensual definition of fatigue**
- ✓ Fatigue is usually seen as a **physical and/or mental exhaustion**
- ✓ Fatigue is often multifactorial and can be triggered by
 - ✓ Lifestyle factors
 - ✓ Stress
 - ✓ Medications
 - ✓ Overwork
 - ✓ Mental and physical illness or disease



physical and/or mental exhaustion



How common is fatigue in SLE ?

Significant fatigue: 68% of 570 SLE patients

Major fatigue

+++

37%

No significant fatigue

33%

Moderate fatigue

14%

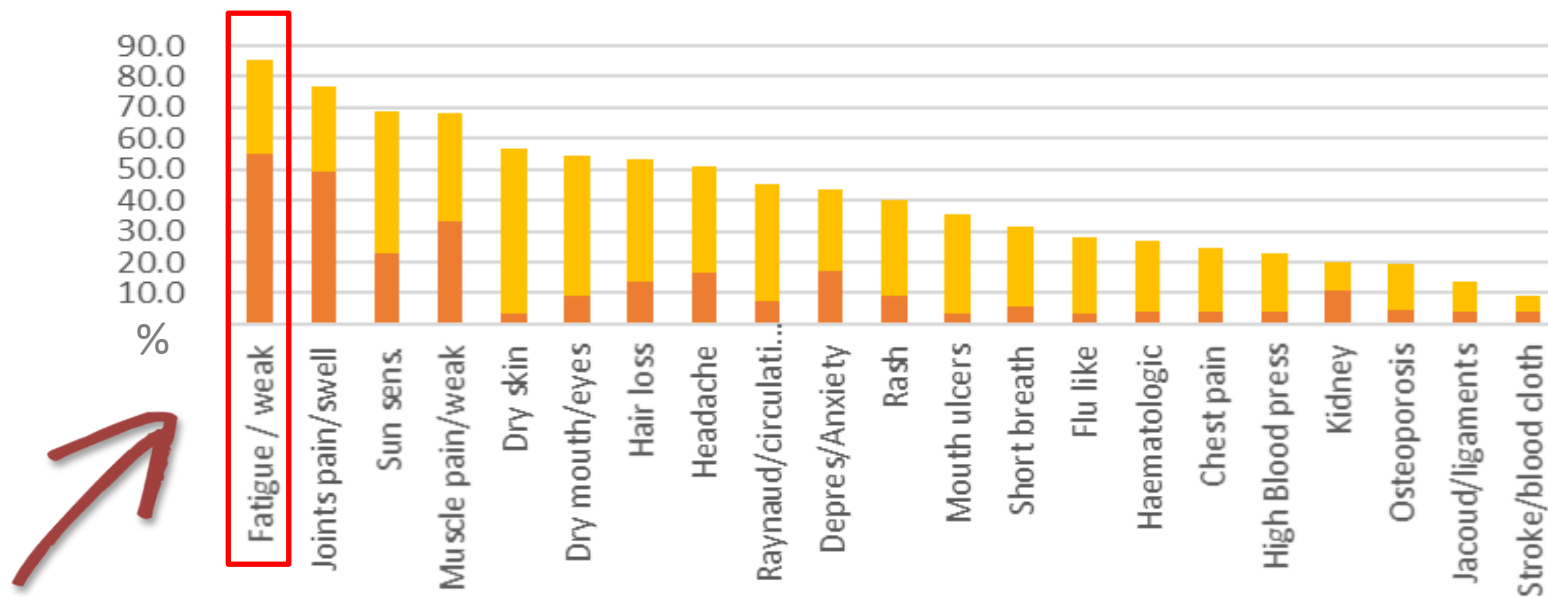
Minor fatigue

17%

Arnaud et al. Rheumatology (Oxford) 2019

LUPUS EUROPE SURVEY 2020 « Living with lupus »

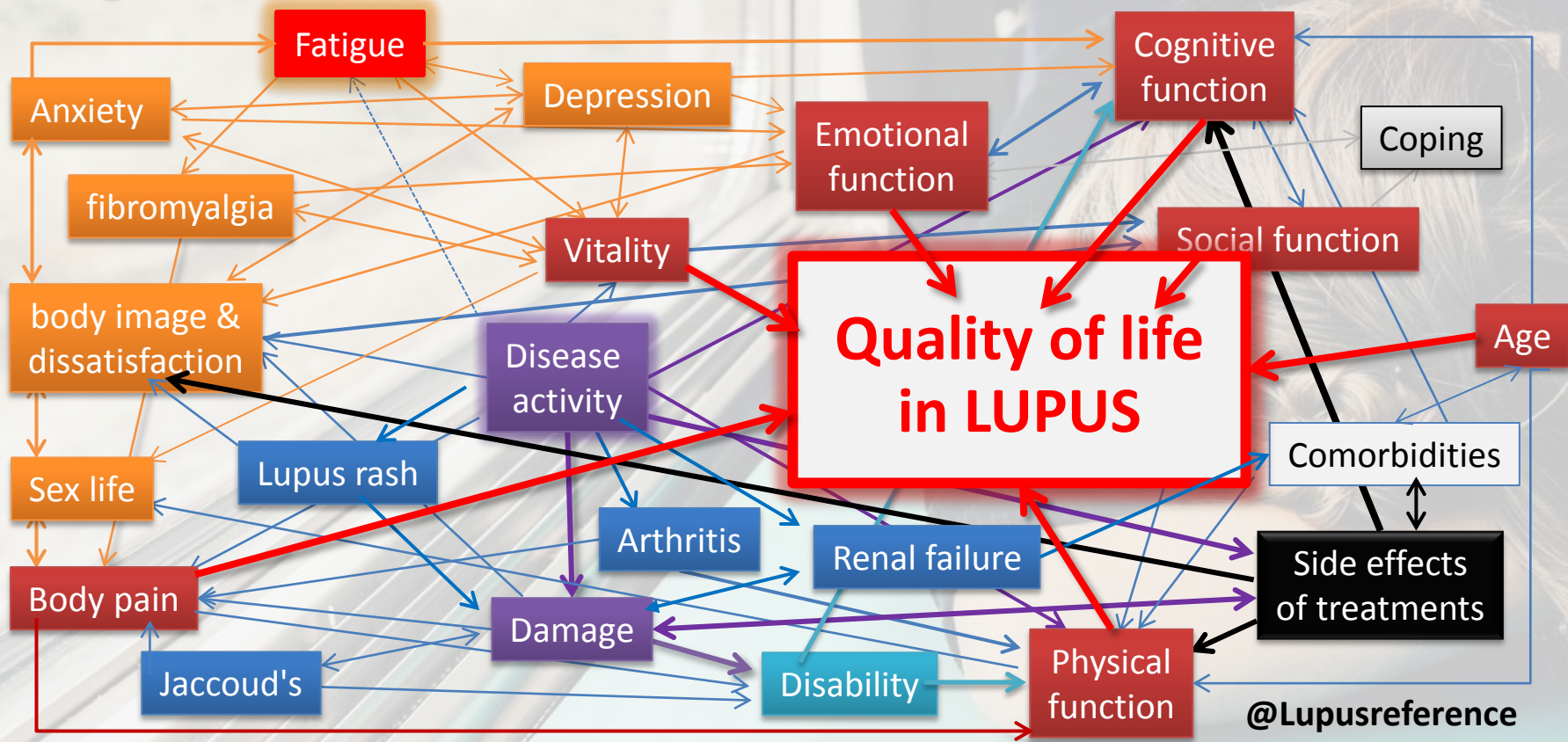
4197 participants
from 35 European countries



Fatigue is the most common and most bothering manifestation associated with SLE

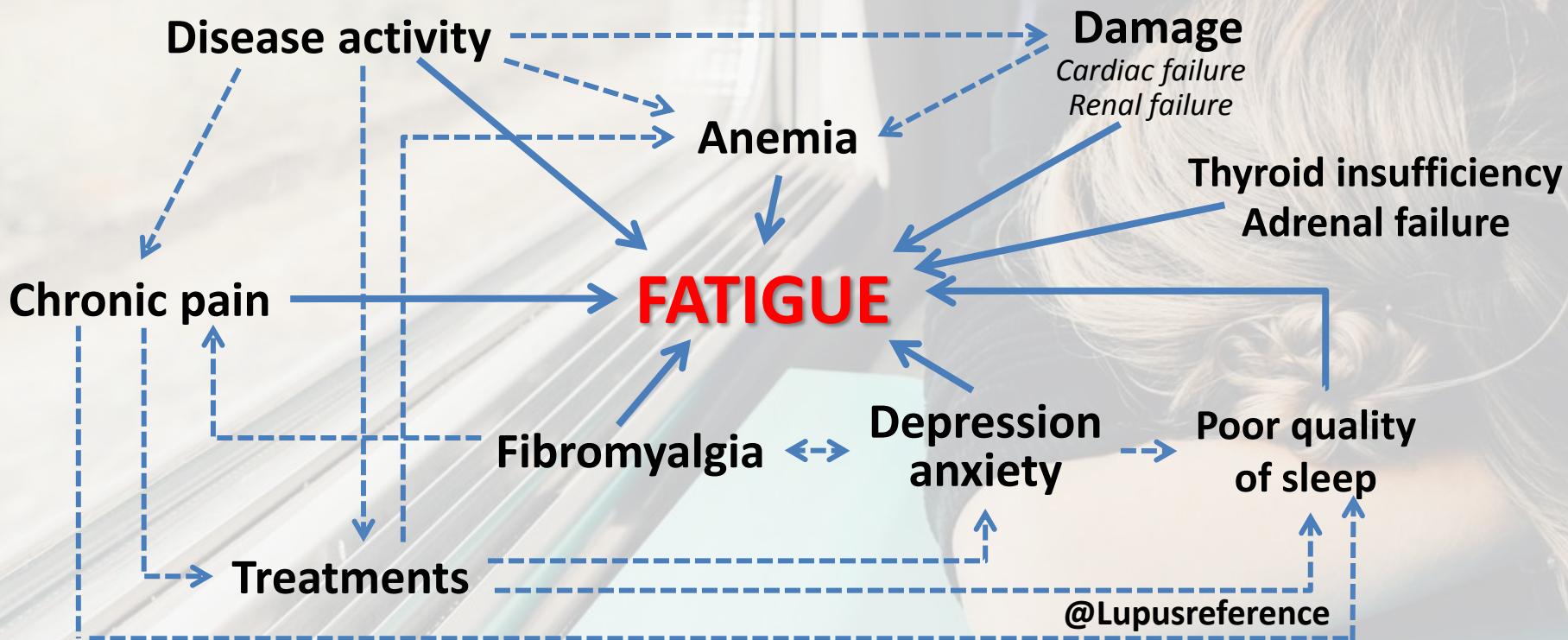
www.Lupus-Europe.org

Fatigue in SLE is associated with a low quality of life



@Lupusreference

What are the determinants of fatigue in SLE?



What are the main determinants of fatigue in SLE?

570 SLE patients assessed for fatigue (the FATILUP study)

Parameters	Univariate	Multivariate	
	p-value	p-value	OR (95%CI)
Age (years); median (IQR)	0.02	0.03	1.01 (1.00 – 1.03) [§]
Female; n (%)	0.15	-	-
BMI (kg/m ²); median (IQR)	0.29	-	-
Definite anxiety; n (%)	<0.0001	<0.0001	4.49 (2.60 – 7.77)
Definite depression; n (%)	0.0003	0.01	4.72 (1.39 – 16.05)
Disease activity (SELENA-SLEDAI); median (IQR)	0.04	0.043	1.05 (1.00 - 1.12)[§]
Hydroxychloroquine; n (%)	0.97	-	-
Glucocorticoids (any dose); n (%)	0.02	0.04	1.59 (1.05 – 2.41)
Any IS*; n (%)	0.37	-	-
Physical activity (>3h per week), n (%)	0.02	0.15	0.69 (0.42-1.15)

Fatigue was associated with disease activity (±) & anxiety & depression (+++)

[§]Mean SLEDAI in FATILUP: 2 (0-10)

Arnaud et al. Rheumatology (Oxford) 2019

Pain is an important determinant of fatigue in SLE

In the FATILUP study, we found that **PAINFUL** lupus manifestations were associated with more fatigue

Chronic pain

FATIGUE

Adrenal failure

Depression

Poor quality

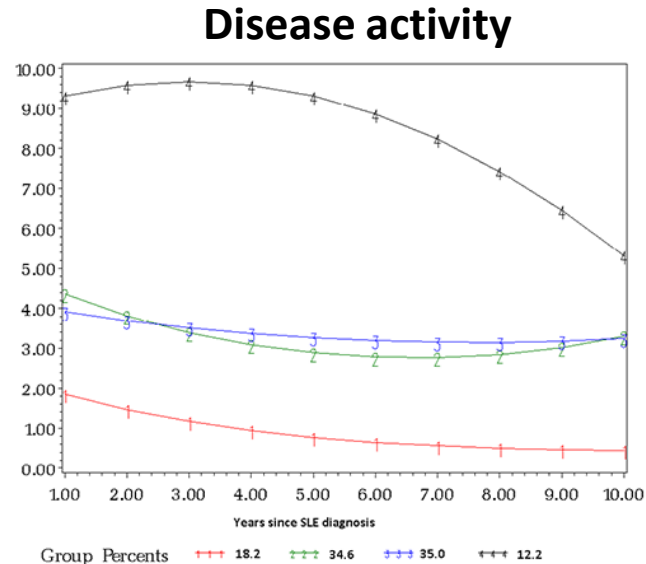
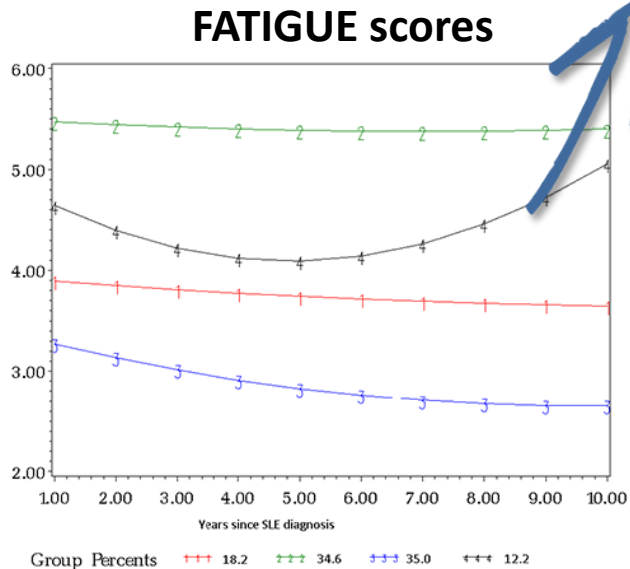
CHRONIC PAIN management is absolutely crucial for the management of fatigue in SLE

@Lupusreference

What is the relationship with disease activity in SLE

Dual trajectories of fatigue and disease activity in an inception cohort of adults with systemic lupus erythematosus over 10 years

Fatigue and disease activity follow distinct trajectories and disease activity alone cannot fully explain fatigue trajectories.



- Trajectories with higher fatigue scores were associated with more fibromyalgia
- Trajectories with higher disease activity were associated with higher cumulative glucocorticoid use.

Touma et al. Lupus 2021

Is fibromyalgia common in patients with SLE?

Prevalence of fibromyalgia in SLE cohort studies

Author	Year	Country	Prevalence
Huang et al.	2020	Australia	26%
Torrente-Segarra et al.	2016	Spain	6.2%
De Araujo et al.	2015	Brazil	12%
Iannuccelli et al.	2012	Italy	18%
Wolfe et al.	2009	USA	21.1%
Valencia-Flores et al.	2004	Mexico	9.5%
Friedman et al.	2003	USA	5%
Ostuni et al.	2002	Italy	1%
Gräfe et al.	1999	Germany	17%

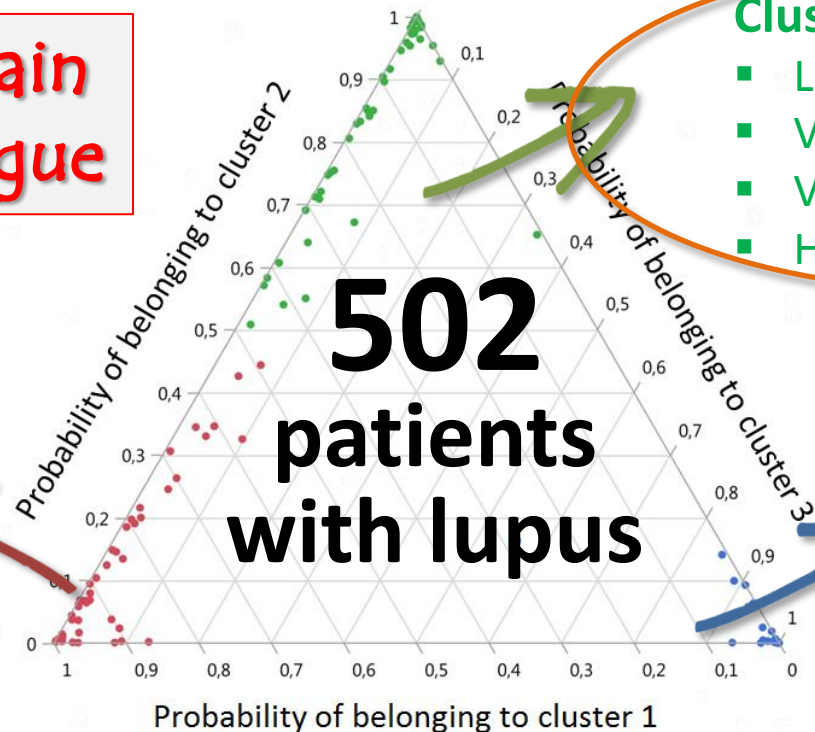
Fibromyalgia is common in SLE patients. Attribution of symptoms to SLE can be difficult because of the pain associated with fibromyalgia

What are the profiles of fatigue in systemic lupus?

We found 3 main profiles of Fatigue

Cluster #1 (67.5%)

- Low disease activity
- Moderate fatigue
- Low anxiety
- Low depression



Cluster #2 (25.3%)

- Low disease activity *Most difficult to treat*
- Very high fatigue
- Very high anxiety
- High depression

Cluster #3 (7.2%)

- High disease activity
- High fatigue
- Low anxiety
- No depression

Arnaud et al. Rheumatology 2020

How can we improve fatigue in SLE?

Intervention	References	Impact on fatigue
Medical treatment <i>Immunosuppressive agents</i>	Strand et al. Arthritis Care Res 2019 Petri et al. Lupus 2017 Yokogawa et al. Arthritis Rheum 2016	In patients active disease, improving disease activity is associated with significant improvement of fatigue in randomized controlled trials of belimumab (Strand), blisibimod (Petri), hydroxychloroquine (Yokogawa) but this effect is likely to be observed with any treatment improving disease activity in SLE although this is not formally proven
<i>N-acetylcysteine</i>	Lai et al. AR 2012	Randomized trial showing improvement of fatigue with NAC 2.4 gm or 4.8 gm/day
Physical exercise	Avaux et al. Acta Clin Belg. 2016	Randomized trial showing that both supervised training and home training improve significantly fatigue in SLE.
Vitamin D	Lima et al. Arthritis Care Res 2016	Randomized, double-blind, placebo-controlled, 24-week trial of oral cholecalciferol 50,000 IU/week in juvenile-onset SLE showing significant improvement of fatigue.
Patient education (Web-based education and counselling)	Kankaya et al. Lupus 2020	Randomized controlled trial of web-based education for the first three months and then counselling and information updates for the next three months showing significant improvement in fatigue.
Transcutaneous auricular vagus nerve stimulation	Aranow et al. ARD 2020	Patients with SLE and pain were randomised to receive transcutaneous auricular vagus nerve stimulation or sham (mimic) stimulation for 4 days, leading to a significant decrease in pain and fatigue.

Interventions NOT improving fatigue in SLE?

Fish oil	Arriens et al. Nutr J 2015	Randomised, placebo-controlled study in 50 SLE patients who received fish oil supplementation or olive oil placebo showing no significant effect on fatigue
DHEA	Hartkamp et al. ARD 2010	Double-blind, randomised, placebo-controlled study in 60 female patients with inactive SLE who received 200 mg oral DHEA or placebo showing no significant effect on fatigue



No significant effect



Management of FATIGUE in Systemic Lupus Erythematosus

If possible, assess fatigue using validated PROs in SLE, such as FACIT-F or FSS

ALWAYS check for common medical causes

Hb, creatinine, fasting glucose, transaminases, calcium, TSH, 8am-cortisol*

Presence of ACTIVE SLE disease?

Yes

No

CONTROL DISEASE ACTIVITY

SLE activity is a major cause of fatigue

also check for intricate causes

Search for intricate causes:

Major damage (e.g. heart failure)?

Chronic pain?

Anxiety, depression?

Sleep apnea?

Reassess FATIGUE

Targeted interventions

(including physical activity)

*In patients who stopped or tapered GCs <5mg/day during the last 6 months

@Lupusreference

Summary about fatigue in SLE

- ✓ Fatigue is experienced by 2/3^{rds} of patients with lupus and severe fatigue by 1/3
- ✓ Fatigue is the most common and most bothersome manifestation of lupus
- ✓ Fatigue is multifactorial, and can be due to:
 - ✓ Disease activity, especially painful manifestations (arthritis, etc...)
 - ✓ Psychological determinants (anxiety, depression +++)
 - ✓ Well-known medical causes: anemia, hypothyroidism, adrenal failure, etc...
 - ✓ Disease damage such as renal or cardiac failure
- ✓ Up to 25% of patients have very high fatigue scores, without significant disease activity. In those patients, anxiety and depression are typically very high
- ✓ Fibromyalgia & chronic pain are significant determinants of fatigue in SLE
- ✓ Validated interventions include: adequate control of disease activity, physical exercise, vitamin D supplementation, management of anxiety/depression/pain

Fatigue in systemic lupus

An evidence-based update in 2021

Pr. Laurent ARNAUD

Department of Rheumatology

National Reference Center for Systemic Autoimmune Diseases, Strasbourg, France

Twitter: [Lupusreference](#)