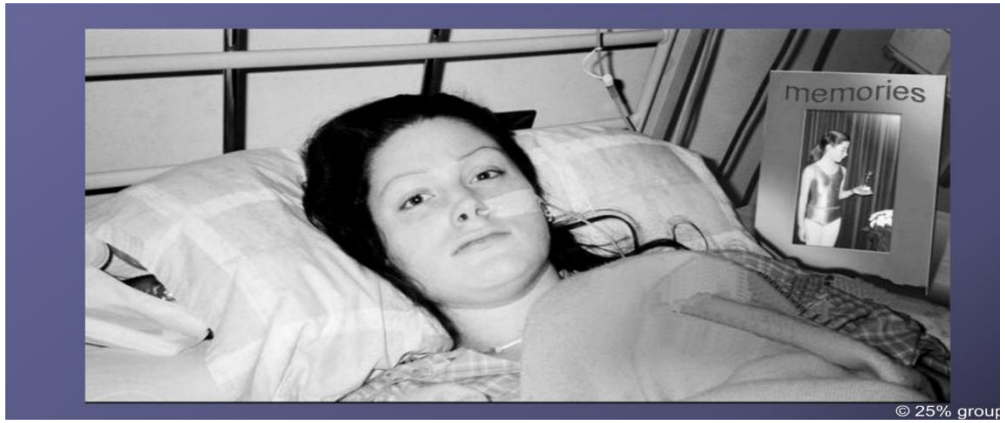
# Nytt lys på ME

*Oppsummering av nokon av dei siste biomedisinske forskningsfunna*

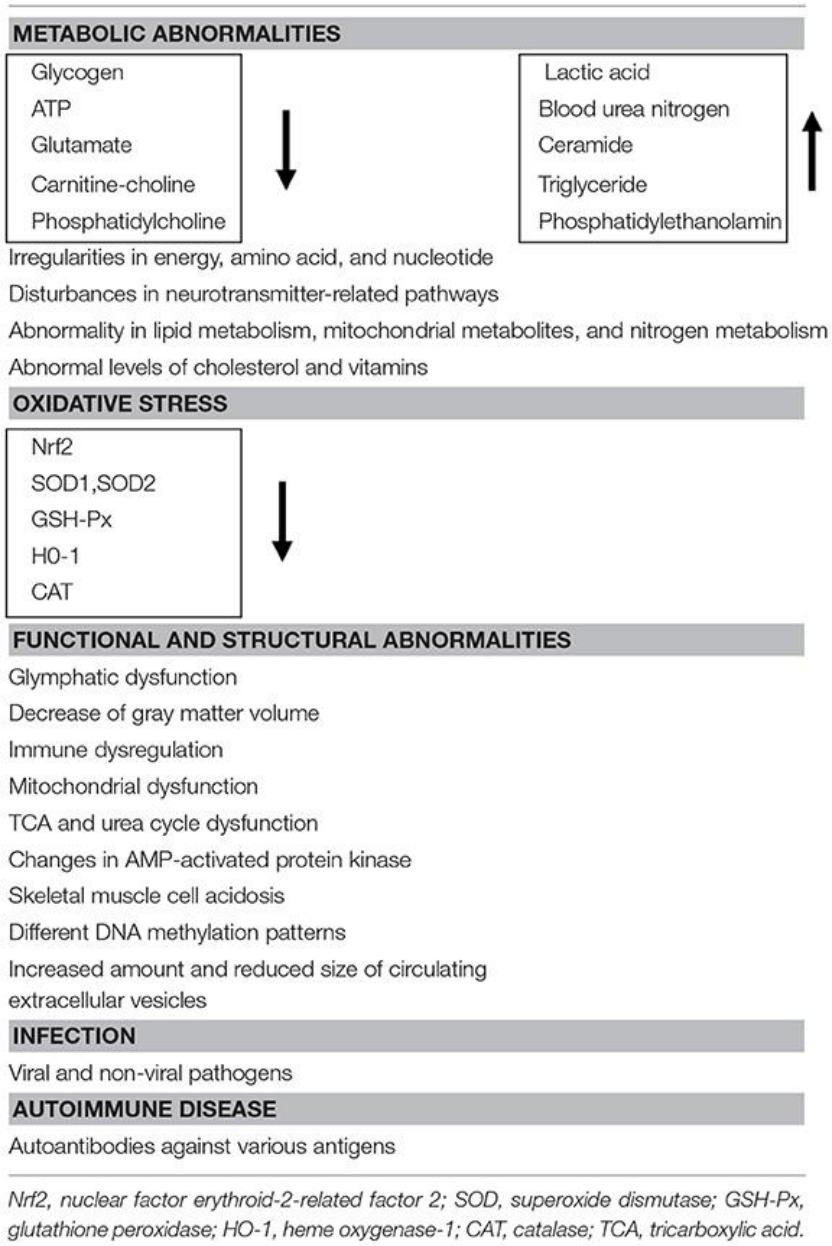
Ola Didrik Saugstad
Pediatrisk Forskningsinstitutt
UiO og OUS

Stryn, 26 mars 2019



# Hvor er forskningen ved ME?

## Oppsummering av forskningsfunn relatert til ME




*Noda M et al Frontiers in Psychiatry 2018;9:589-*


**Lytt til ME-pasientene! | Ola Didrik Saugstad**
ME er en betennelsestilstand som rammer flere organer, også hjernen, og immunsystemet er aktivert.
**DEBATT** 21. sep. 2017
**Ola Didrik Saugstad** Professor 1 i Pediatri, Universitetet i Oslo. Det er en «latterlig holdning» at ME i utgangspunktet er psykologisk, slås det fast i en amerikansk studie.

**Tysnes** **Owe**

**ME er ikke en betennelse i hjernen | Tysnes og Owe**
Professor Saugstad bruker sin medisinske autoritet til å undertrykke pasienter som er blitt friske og vil dele sin erfaring.
**DEBATT** 28. sep. 2017 **Ole-Bjørn Tysnes (overlege/professor) og Jone Furlund Owe (overlege, PhD)**
**Nevrologisk avdeling, Haukeland Universitetssykehus**

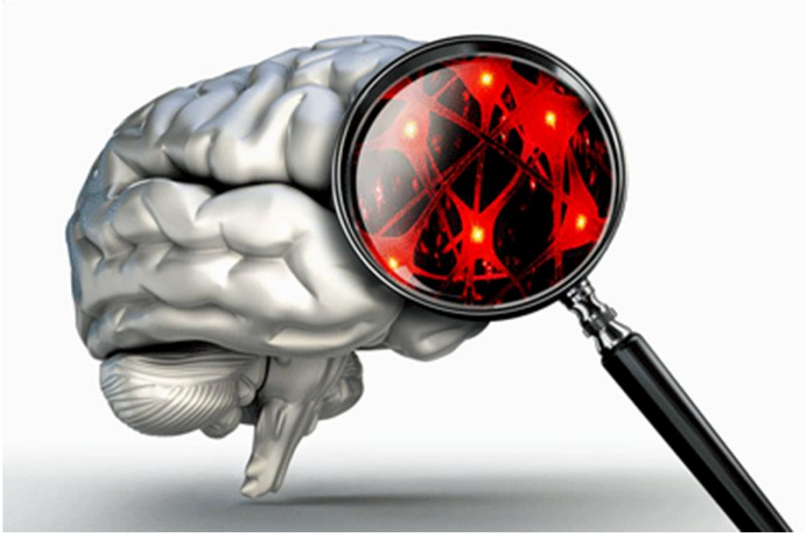
**«ME er en alvorlig, fysisk, kronisk og kompleks multisystemsykdom» | Ola Didrik Saugstad**
Jeg har aldri utropt meg til ME-ekspert, men jeg har et dypt engasjement for pasientene som føler seg ignorert eller feilbehandlet
**DEBATT** 3. okt. 2017 **Ola Didrik Saugstad** Professor 1 i Pediatri, Universitetet i Oslo

# Er det en inflammasjon i sentralnervesystemet ved ME?

«Brain on fire»

Neuroinflammation was found to be widespread in the brain areas of the patients with ME/CFS and was associated with the severity of their neuropsychological symptoms.

*Watanabe Y  brain and Nerve, 2018*



Neuroinflammation in CSF/ME is one of the main topics to be studied by NIH, USA

*Nature 2018*

Neuroinflammasjon og CFS/ME i en PET studie fra Japan

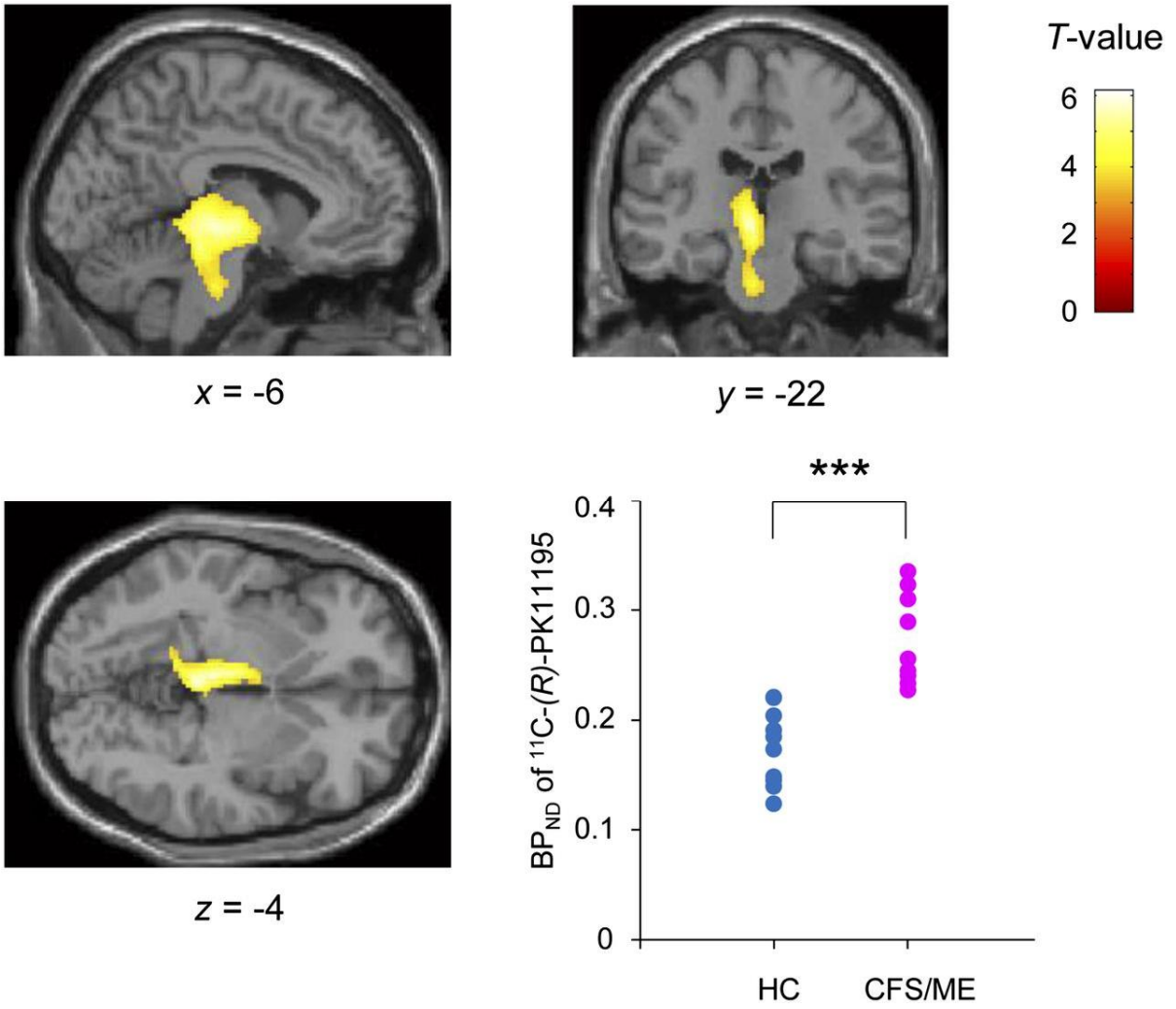
Our results provide evidence of neuroinflammation in CFS/ME patients, as well as evidence of the possible contribution of neuroinflammation to the pathophysiology of CFS/ME.

**Nakatomi Y et al Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An $^{11}$C-(*R*)-PK11195 PET Study. J Nuclear Med 2014;55:945-50**

Demographic and Clinical Characteristics of All Participants

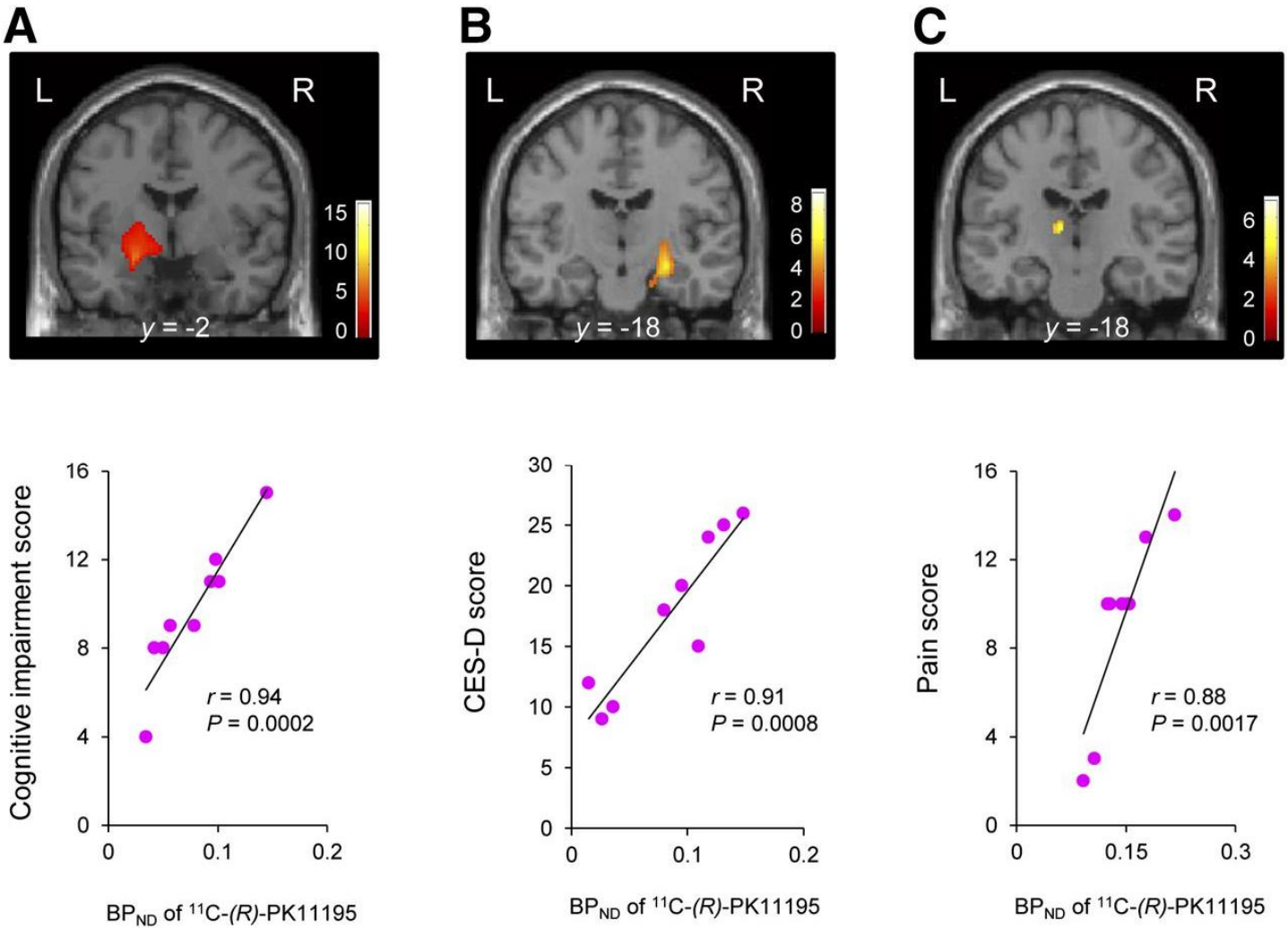
| Characteristic | CFS/ME (*n* = 9) | Healthy control (*n* = 10) | *P* |
|---|---|---|---|
| Age (y) | 38.4 ± 5.1 | 39.1 ± 6.0 | 0.8030 |
| Sex (F/M) | 6/3 | 7/3 | 0.8843 |
| Disease duration (y) | 5.2 ± 7.3 | | |
| VAS of fatigue sensation (score) | 60.4 ± 24.2 | 27.3 ± 23.2 | 0.0074 |
| Chalder fatigue scale (score) | 21.9 ± 7.1 | 10.9 ± 5.0 | 0.0011 |
| Cognitive impairment (score) | 9.6 ± 3.1 | 4.0 ± 3.0 | 0.0013 |
| Pain (score) | 9.1 ± 4.0 | 2.2 ± 1.8 | 0.0001 |
| CES-D (score) | 17.6 ± 6.5 | 7.5 ± 5.6 | 0.0020 |

*Nakatomi Y et al. J Nucl Med 2014;55:945-950*




Statistical parametric maps of BPND of 11C-(R)-PK11195 in CFS/ME patients and healthy controls.
Yasuhito Nakatomi et al. J Nucl Med 2014;55:945-950

JNM The Journal of NUCLEAR MEDICINE




Relationships between 11C-(R)-PK11195 BPND and neuropsychologic symptoms in CFS/ME patients.
Yasuhito Nakatomi et al. J Nucl Med 2014;55:945-950

# USA 2015: ME/CFS er en Biologisk sykdom

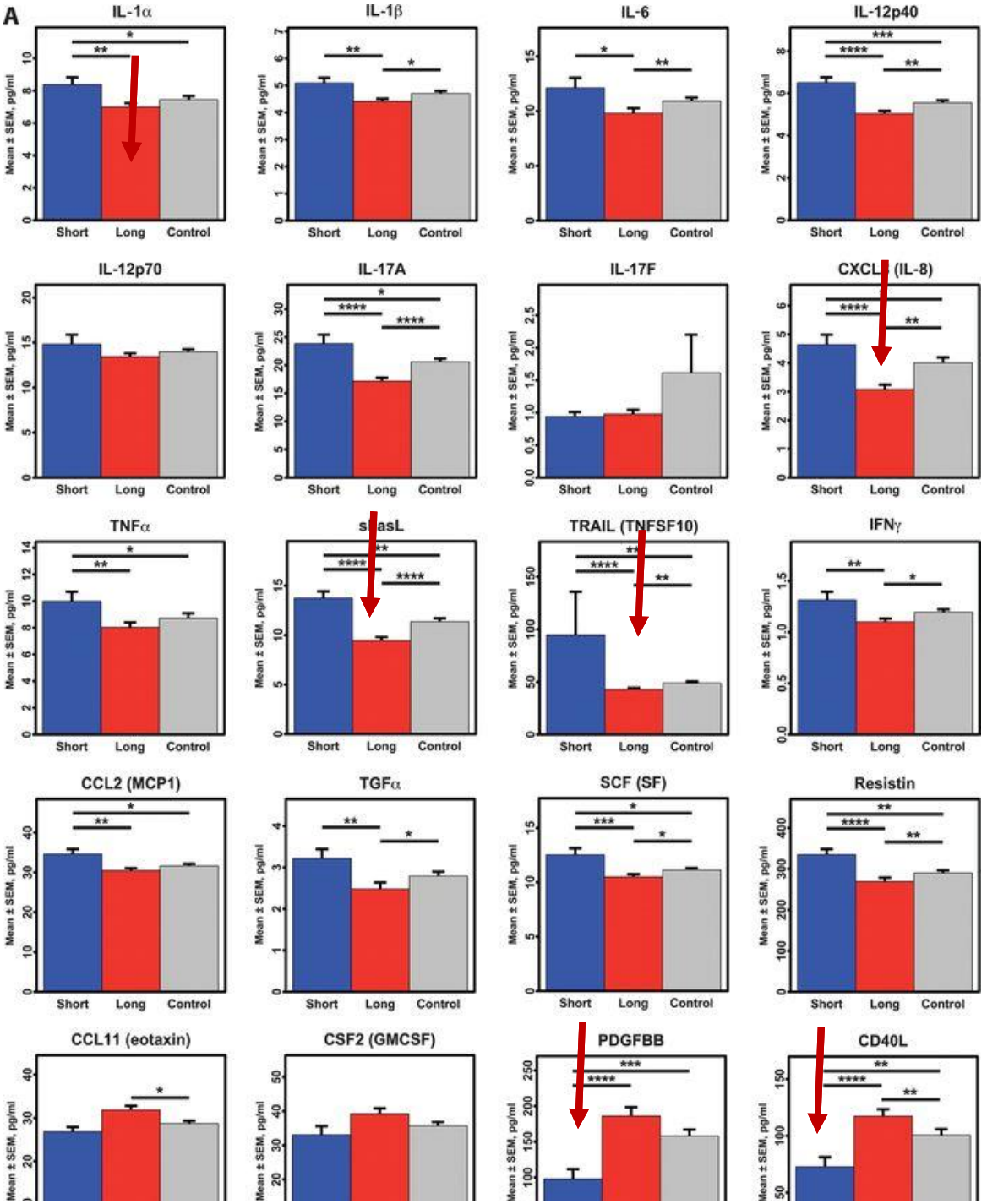
## USA forskere hevder å ha robust evidens for at ME/CFS  er en biologisk sykdom |

Columbia University press release | 27 February 2015

**Researchers at the Center for Infection and Immunity at Columbia Universityôs Mailman School of Public Health identified distinct immune changes in patients diagnosed with chronic fatigue syndrome, known medically as myalgic encephalomyelitis (ME/CFS).**

These immune signatures represent the first robust physical evidence that ME/CFS is a biological illness as opposed to a psychological disorder, and the first evidence that the disease has distinct stages.

Cytokiner i blodplasma
Hos ME pasienter med kortvarig versus langvarig Sykdomsforløp
Friske kontroller til sammenligning




**Comparison of plasma cytokine levels in short-duration ME/CFS, long-duration ME/CFS, and control subjects.**

**Mady Hornig et al. SciAdv 2015;1:e1400121**

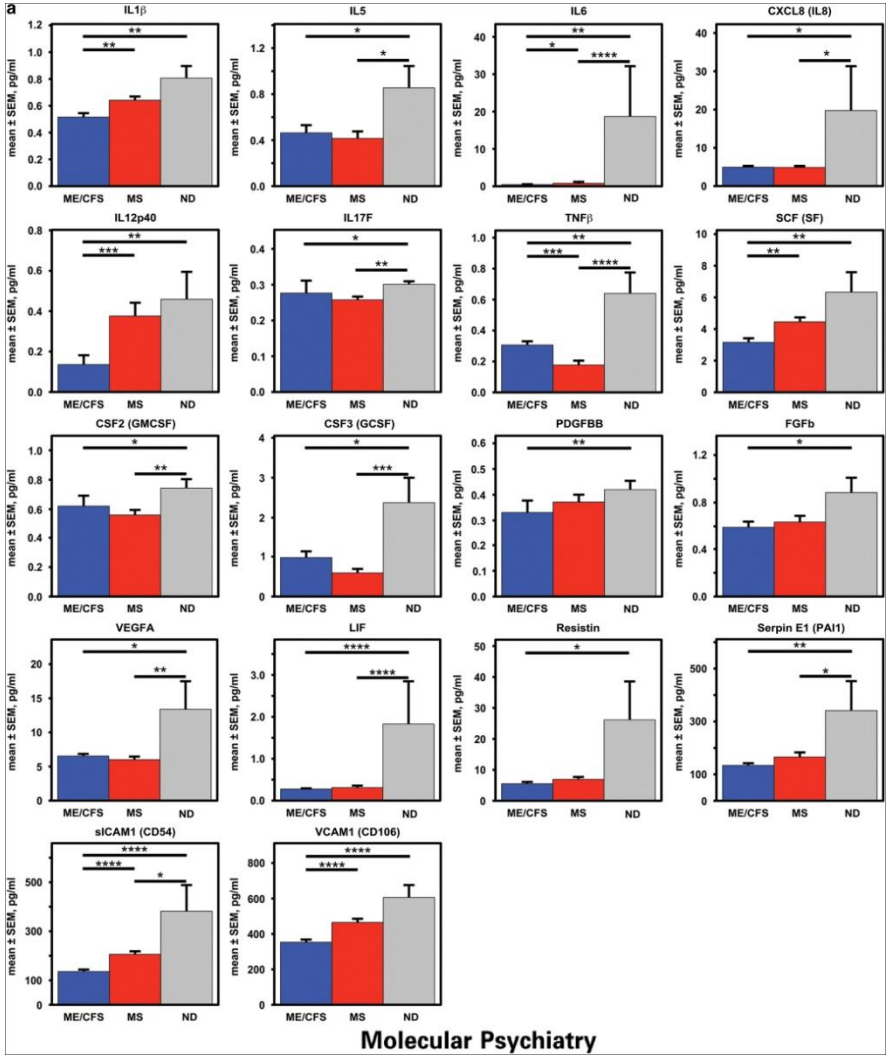
# Cytokiner i Cerebrospinalvæsken ved ME/CFS vs MS og friske kontroller

ME:

- Endrede cytokin profiler som i retning av autoimmun sykdom
- Infeksjoner med virus og bakterier
- Sentralnervesystem dysfunksjon
- Cerebral hypoperfusjon
- Kronisk inflammasjon i hvit hjernesubstans

***Resultatene våre tyder på en markert forstyrret immun signatur i cerebrospinal væsken ved ME/CFS.***

***Det er i overenstemmelse med en immunaktivering av sentralnervesystemet***




*Hornig M et al Molecular Psychiatry* advance online publication 31 March 2015. doi:10.1038/mp.2015.29

ÅThey found specific patterns in patients who had the disease **three years or less** that were not present in controls or in patients who had the disease for more than three years. Short duration patients had increased amounts of many different types of immune molecules called cytokines.

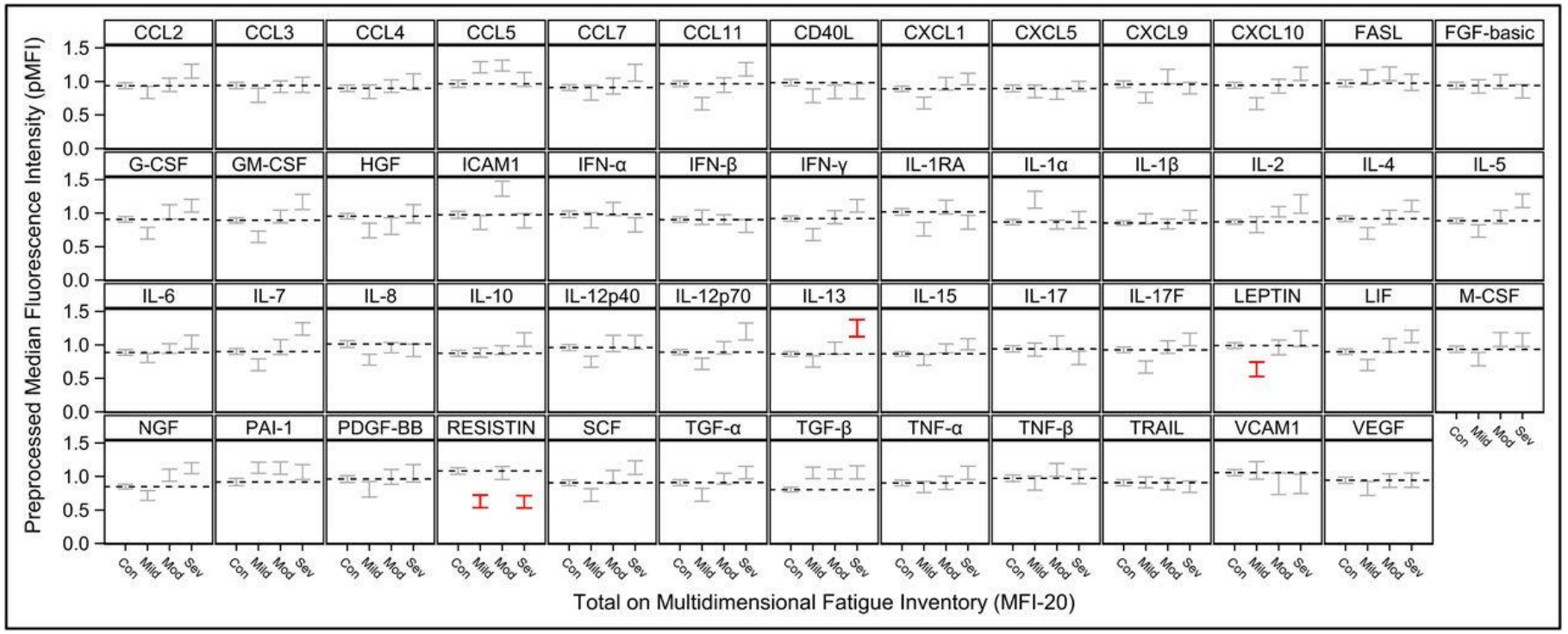
ÅThe association was unusually strong with a cytokine called **interferon gamma** that has been linked to the fatigue that follows many viral infections, including Epstein-Barr virus

**"Vi har nå evidens som bekrefter det millioner med denne sykdommen allerede vet, at ME/CFS ikke er psykologiò**

ñWe now have evidence confirming what millions of people with this disease already know, that ME/CFS isnôt psychologicalò

states lead author **Mady Hornig,** MD, director of translational research at the Center for Infection and Immunity and associate professor of Epidemiology at Columbiaôs Mailman School.

Cytokine signature associated with disease severity in chronic fatigue syndrome patients

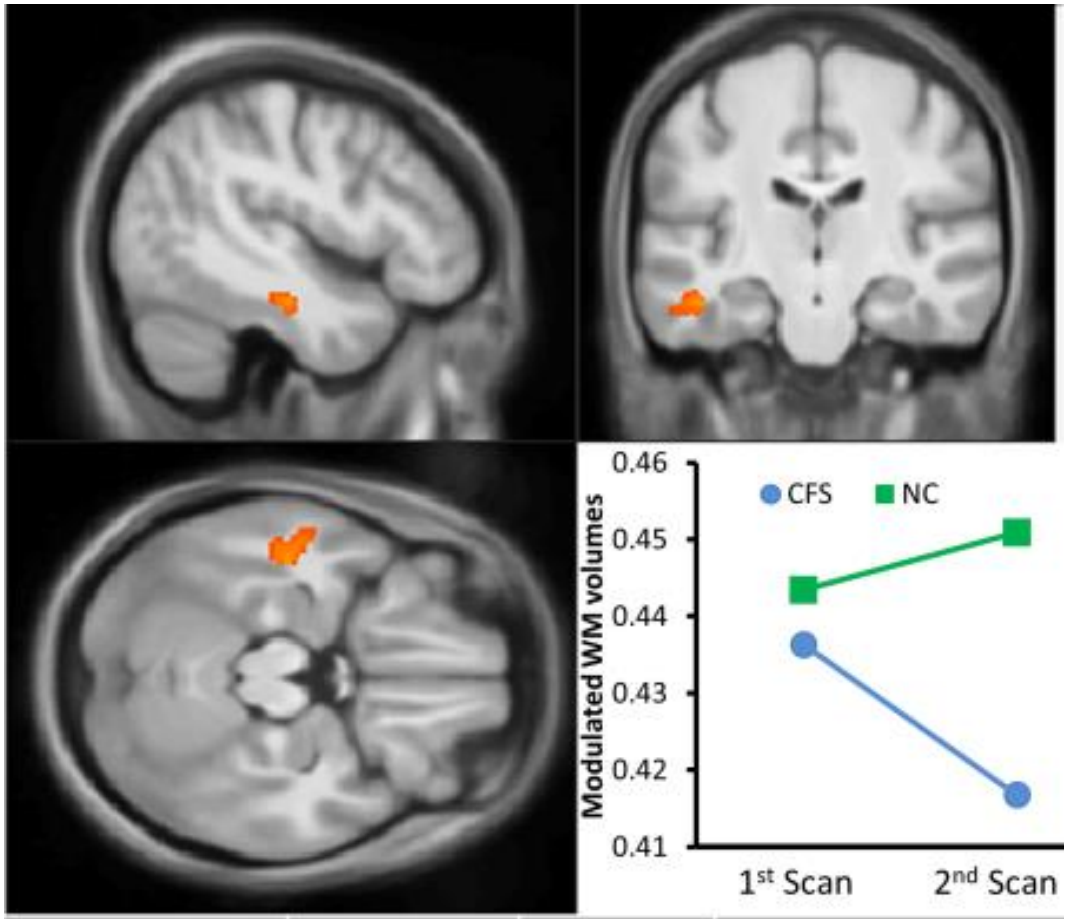



Although only two cytokines were found to be different (TGF-ƀ higher and resistin lower) in ME/CFS patients compared with controls, 17 cytokines correlated with ME/CFS severity. Thirteen of these cytokines are proinflammatory and may contribute to many of the symptoms these patients experience for several years.

*Montoya JG et al Proc Natl Acad Sci U S A. 2017; 114(34): E7150ï E7158*

# Progressiv hjerneforandring

## Reduksjon i hvit substans ï  Hos CSF/ME Pasienter




| $P_{FWE\_corr\_cluster}$ | k | T | MNI Coordinates |
|---|---|---|---|
| 0.03 | 431 | 4.91 | -45 -20 -20 |

**MR utført med 6 års mellomrom**
**15 CFS/ME pasienter (CFS)**
**10 Normale kontroller (NC)**

**Adelaide, Australia**

**Shan ZY et al  Progressive brain changes in patients with chronic fatigue syndrome: A longitudinal MRI study. J of Magnetic Resonance Imaging** 28 APR 2016 DOI: 10.1002/jmri.25283

# Diagnosen

- Diagnosekriterier
- Diagnostiske tester - Biomarkører

# Symptomer

- Kardiale og kardiovaskulære
- Hormonelle
- Immunologiske
- Respiratoriske
- Gastrointestinale
- Blod og koagluasjonsproblemer

**Utmattelse / Energisvikt står sentralt i symptombildet**

**Ingen relasjon til psykiske lidelser, men pasientene kan få en reaktiv depresjon eller andre psykiske problemer sekundært til belastningen med å ha en alvorlig invalidiserende sykdom.**

**ME pasienter har en annen personlighetsprofil enn depresjonspasienter**

***Pasientene føler seg avvist og mistrodd av omgivelsene inkl helsevesenet***

# Mer enn 20 Forskjellige definisjoner på ME

- **1988: *CDC Holmes* Ny sykdom? Forskningsdefinisjon**

- **1991: *Oxford*** Bygger ikke på observerbare sykdoms-tegn, men på tolkningen av de subjektive symptomer. Økt trettbarhet ikke inkludert. Psykosomatisk. Inkluderer også psykiatriske lidelser (IKKE PEM).

- **1994: *CDC Fukuda*** Kompromiss mellom psykosomatikken og somatikken. (IKKE PEM)

- **2003: *Canada*** Mer somatisk orientert. Inkluderer økt trettbarhet (PEM)

- **2011: ICC (International Consensus Criteria)** Utarbeidet av et internasjonalt ekspertpanel fra 13 land og videreutviklet Canadakriteriene.

- **2015: IOM Criteria** (PEM sentralt)

# ME er en biomedisinsk tilstand
# IOM 2015

- **ME/CFS er en alvorlig, fysisk, kronisk og kompleks multisystemsykdom,  som er sterkt funksjonsnedsettende"**

- **Misforståelsen om at sykdommen er psykogen eller en form for somatisering  må opphøre.**

- **ME/CFS er en fysisk sykdom som angriper flere av kroppens  systemer.ò**

- **Vitenskapelig evidens slår fast at det foreligger immundysfunksjon ved ME/CSF**

Årsaken til ME er fortsatt er ukjent, men  ved ME er det:

- Nedsatt evne til å delta i aktiviter som man gjorde før sykdommen ï  varighet mer enn 6 måneder ï ledsaget av nyoppstått kraftig utmattelse

- Forverring etter alle typer anstrengelse inkludert fysisk og emosjonelt stress

- Ineffektiv søvn ï  man våkner u-uthvilt

I tillegg hevder  IOM rapporten at CFS/ME  også inkluderer

enten

*Kognitiv forstyrrelse*

og/eller

*Ortostatisk intoleranse*

# Canada Definisjonen Diagnosekode ICD -10: G93.3

## En pasient med ME skal tilfredstille følgende kriterier:

- **utmattelse, utmattelse eller sykdomsfølelse etter anstrengelse,**
- **søvnproblemer og smerter**
- **to eller flere nevrologiske/kognitive manifestasjoner**
- **ett eller flere symptomer fra to av kategoriene av**
- **autonome, nevroendokrine og immunologiske manifestasjoner**

**Varighet > 6 mnd)**

**Ekskludér aktive sykdomsprosesser som kan forklare de fleste hovedsymptomene**

- ***Utmattelse***
- ***Søvnforstyrrelse***
- ***Smerter***
- ***Kognitiv dysfunksjon***

# ICC: International Consensus Criteria

En ME-diagnose krever at pasienten oppfyller kriterier innen fire kategorier:

a)anstrengelsesutløst nevroimmunologisk energisvikt med til dels betydelig forlenget restitusjonstid,

(b) nevrologiske forstyrrelser (symptomer innen 3 av 4 kategorier:
*kognitiv evne*
*smerte*
*søvnforstyrrelse*
*sensoriske, perseptive eller motoriske affeksjoner*

(c) immunologiske, gastrointestinale eller urogenitale forstyrrelser innen 3 av 5 kategorier bl.a.:
*influensalignende symptomer*
*kvalme*
*overfølsomhet*

(d) forstyrrelser i energiproduksjon og energitransport innen 1 av 4 kategorier:
*kardiovaskulær*
*respiratorisk*
*termoregulatorisk*
*intoleranse for ekstreme temperaturer*.

## IOM criteria for ME/CSF

The core symptoms of ME/CSF

- Substantial reduction or impairment in ability to engange in pre-illness activity that persists for 6 months or more and is accompanied by fatigue. The fatigue is profound not lifelong, not result of ongoing exertion, and not alleviated by rest.

- Post- exertional malaise (PEM) in which physical or mental activities result in a delayed exacerbation of symptoms and reduction in functioning.

- Unrefreshing sleep and a variety of sleep disturbances.

- Either cognitive impairment and/or orthostatic intolerance (the development of symptoms when upright that are alleviated when lying down).

- *These core features must be moderate to severe and present at least 50% of the time; this is key to separating ME/CFS from other common causes of fatigue.*
  *PEM is the clinical hallmark of ME and its most distinctive symptom. PEM can help differentiate ME/CFS from other conditions and has been objectively assosiated with impaired aerobic energy metabolism and orthostatic stress.*

# IOMs kriterier for CFS

## 1.En signifikant reduksjon eller svekkelse

i forhold til før sykdommen i evnen til å delta i:

- Å arbeid, utdanning,sosiale, eller personlige aktiviteter
- Å varighet mer enn 6 måneder
- Å ledsaget av utmattelse, som ofte er Alvorlig.
- Å *Ny eller med et klart definert start-tidspunkt*
  *Som ikke er en følge av pågående uttalt anstrengelse*
  *Som ikke bedres vesentlig av hvile*

2. **PEM: (Post exertional malaise)**
Utmattelse/ubehag etter anstrengelse

## 3. **Ikke oppfriskende søvn**

Og minst en av disse:
Kognitive forstyrrelser
Ortostatisk intoleranse

# Hva er PEM ?

Patients experiencing PEM will often describe a «crash», relapse», or «collapse» after mental or physical exertion that was previously tolerated. It can take hours, days, a wek or even longer to return to the previous baseline after a crash.

***What happens when you engage in normal (previously tolerated) physical or mental exertion?***

***How much activity does it take for you to feel ill or to trigger illness worsening?***

***How long does it take to recover from physical or mental effort?***

***Do you avoid or change certain activities because what happens after you do them?***

# Biomarkør ved ME?

# Biomarkør for ME?

**Now, for the first time, Cornell University researchers report they have identified biological markers of the disease in gut bacteria and inflammatory microbial agents in the blood.**

In a study published June 23 2016 in the journal *Microbiome*, the team describes how they correctly diagnosed myalgic encephalomyeletis/chronic fatigue syndrome (ME/CFS) in 83 percent of patients through stool samples and blood work, offering a noninvasive diagnosis and a step toward understanding the cause of the disease.

"Our work demonstrates that the gut bacterial microbiome in chronic fatigue syndrome patients isn't normal, perhaps leading to gastrointestinal and inflammatory symptoms in victims of the disease," said Maureen Hanson, the Liberty Hyde Bailey Professor in the Department of Molecular Biology and Genetics at Cornell and the paper's senior author.

**"Furthermore, our detection of a biological abnormality provides further evidence against the ridiculous concept that the disease is psychological in origin."**

# Metabolic features of chronic fatigue syndrome

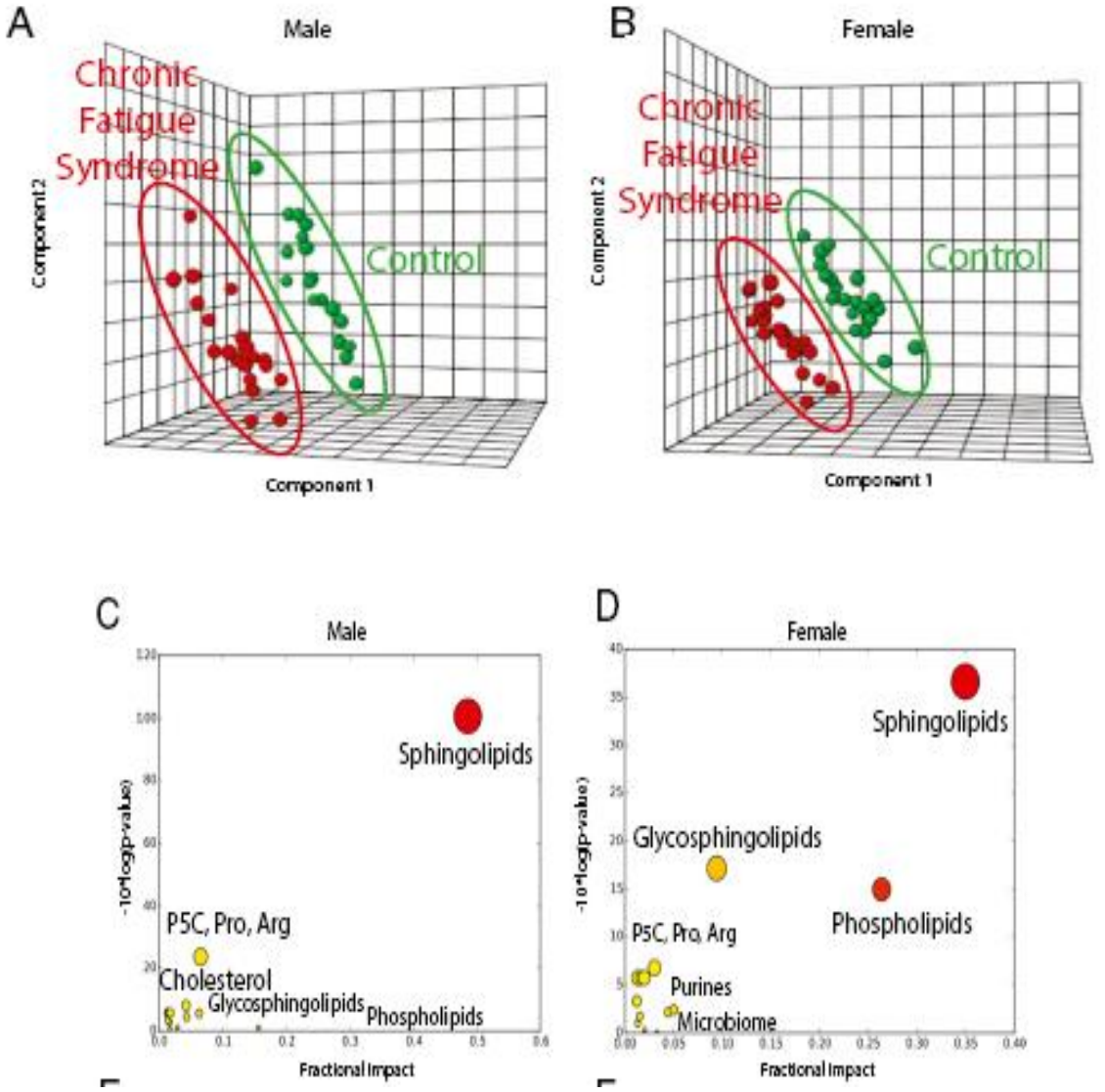
Robert K. Naviaux[a,b,c,d,1], Jane C. Naviaux[a,e], Kefeng Li[a,b], A. Taylor Bright[a,b], William A. Alaynick[a,b], Lin Wang[a,b], Asha Baxter[f], Neil Nathan[f,2], Wayne Anderson[f], and Eric Gordon[f]

**612 metabolitter**
**Hos 45 ME/CFS og**
**39 kontroller**

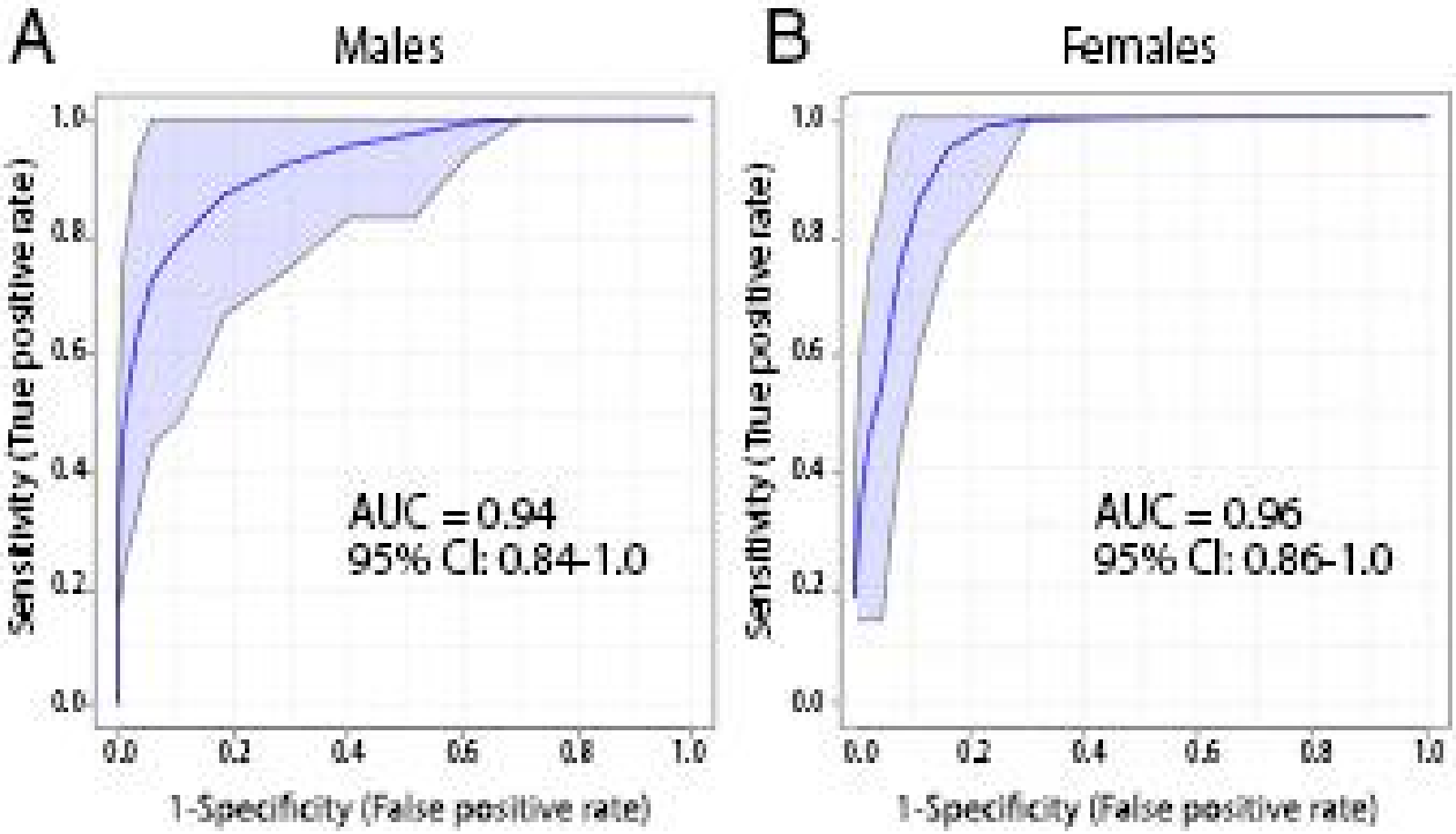
**80% av metabolittene**
**var redusert hos ME/CFS**

**Dette tyder på at ME/CFS pasienter reagerer på ytre stress ved et redusert stoffskifte**

**PNAS, 2016, August**
**pp E5472-E5480**



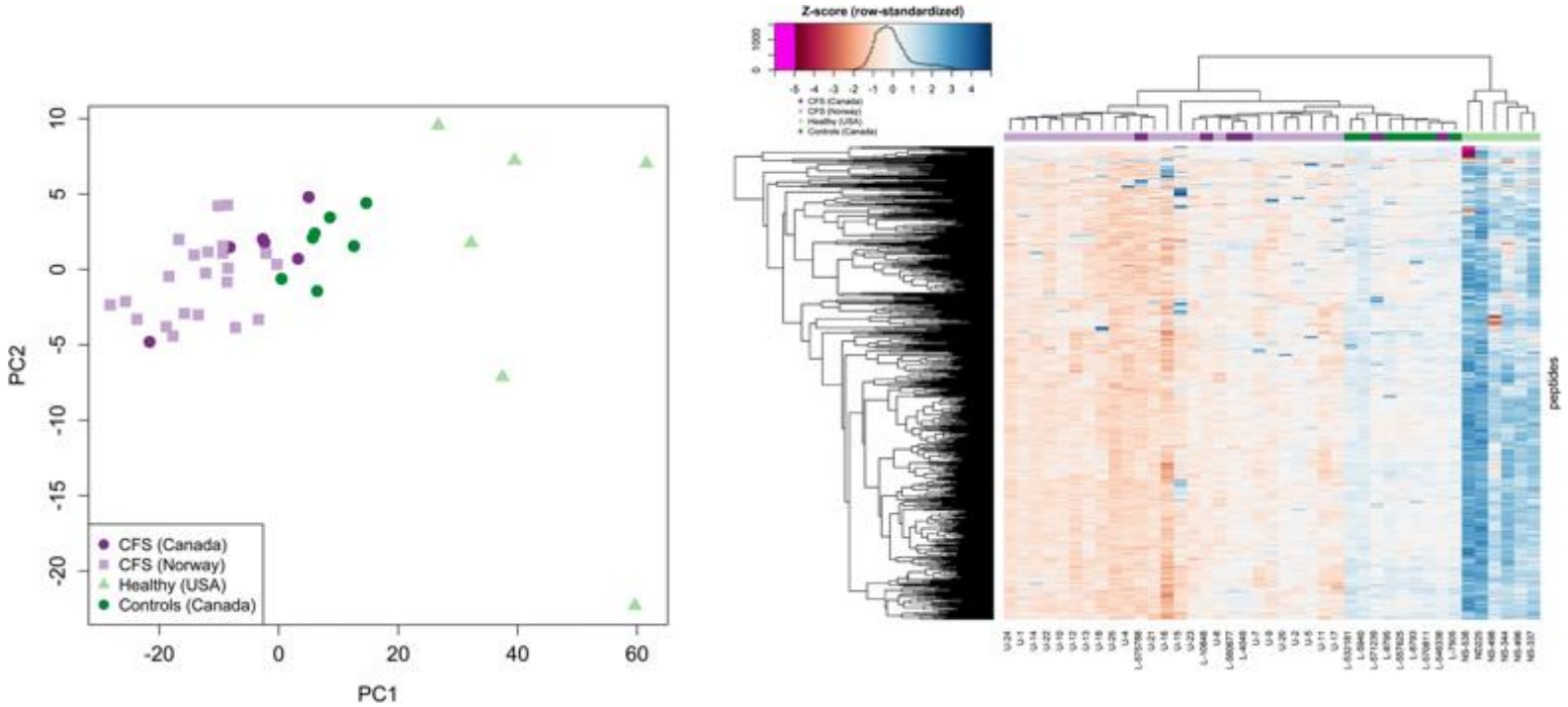
# En biomarkør for ME?




**8 stoffskifteprodukter**

**13 stoffskifteprodukter**

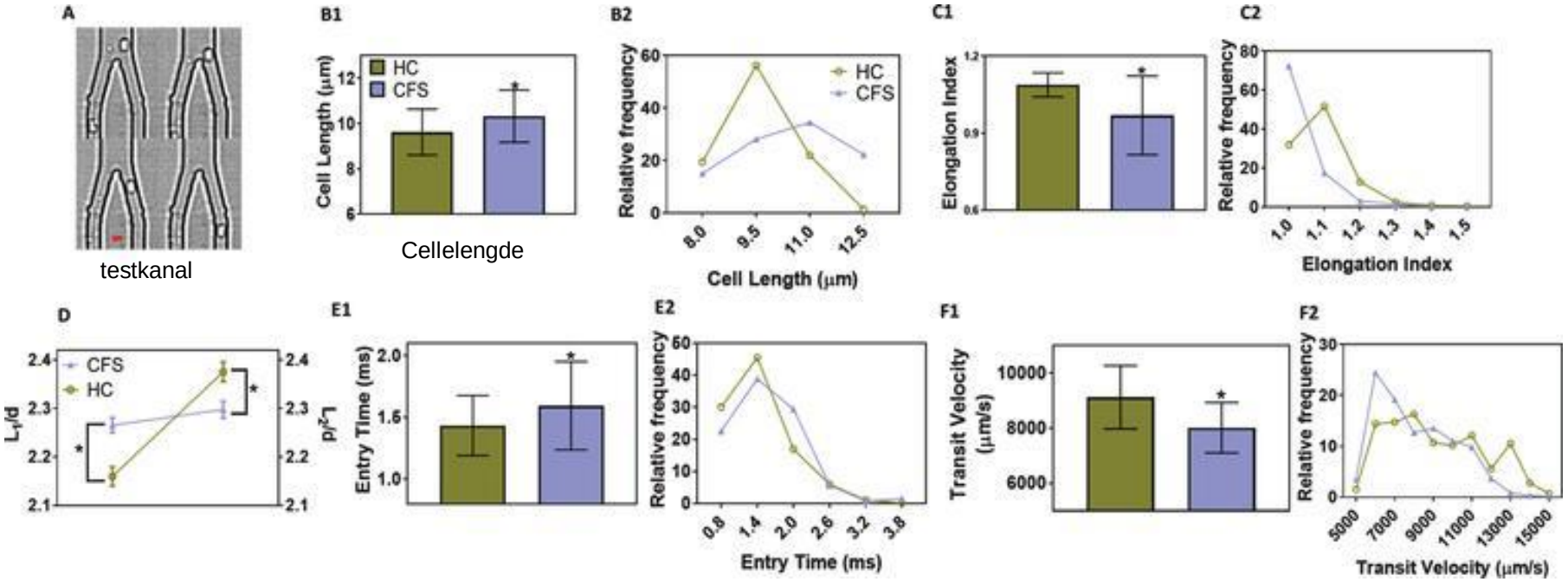
# Immunsignatur analyse ved ME/CFS




256 peptider som skiller ME/CFS fra friske kontroller ï  en fremtidig biomarkør for ME?

Günther OP et al Molecular Neurobiology 2018;

# Nedsatt deformabilitet i røde blodceller ved CFS- en biomarkør ved ME?




**Røde blodlegemer er større og stivere hos ME/CFS enn i friske kontroller noe som kan forklare smerter og fatigue ved ME på grunn av langsommere mikrosirkulasjon og dårligere oksygenering**

**Kan dette brukes som en screening test ved ME?**

*Saha AK, ...Davis RW et al  Clin Hemorheology& Microcircul 2019:71:113-116*

# Hvem er ME pasientene?

# Forekomst av ME

**USA: 800, 000** ***kvinner 522/100,000 menn 291/100,000***
**UK: 240 000**

**Norge 2/1000 blant barn og 3/1000 hos voksne dvs opptil 10,000 ME pasienter i Norge? Ikke alle har diagnosen**

**Danmark: 14 000?**

**Økende i Nord-Europa?**

**ME hyppigere enn MS, HIV, brystkreft (USA)**

# Housebound versus nonhousebound patients with myalgic encephalomyelitis and chronic fatigue syndrome

**Tricia Pendergrast**[1], **Abigail Brown**[1], **Madison Sunnquist**[1], **Rachel Jantke**[1], **Julia L Newton**[2], **Elin Bolle Strand**[3], and **Leonard A Jason**[1]

[1]Center for Community Research, DePaul University, USA

[2]Newcastle University, UK

[3]Oslo University Hospital, Norway

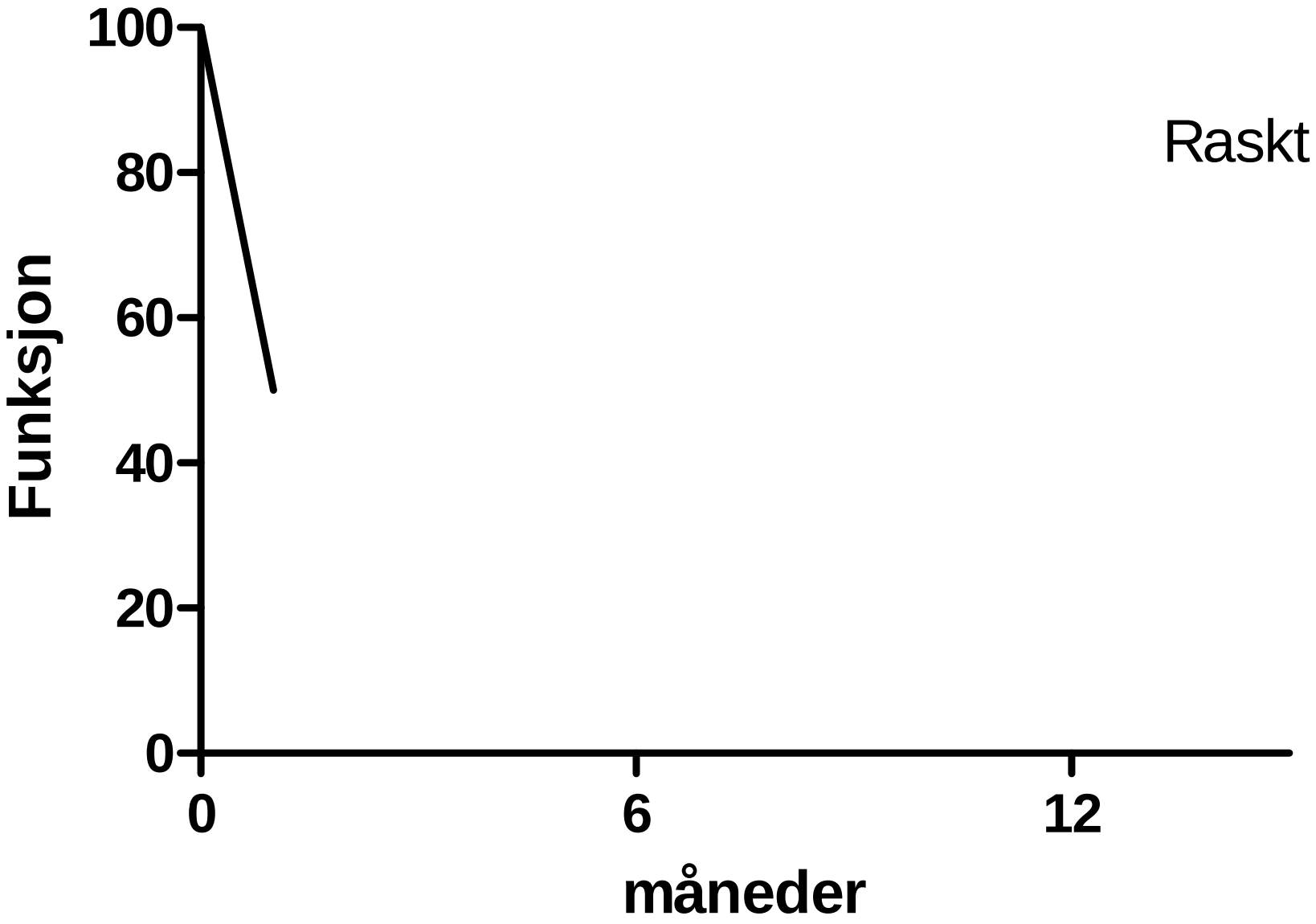
*Chronic Illn*. 2016 December ; 12(4): 292–307.

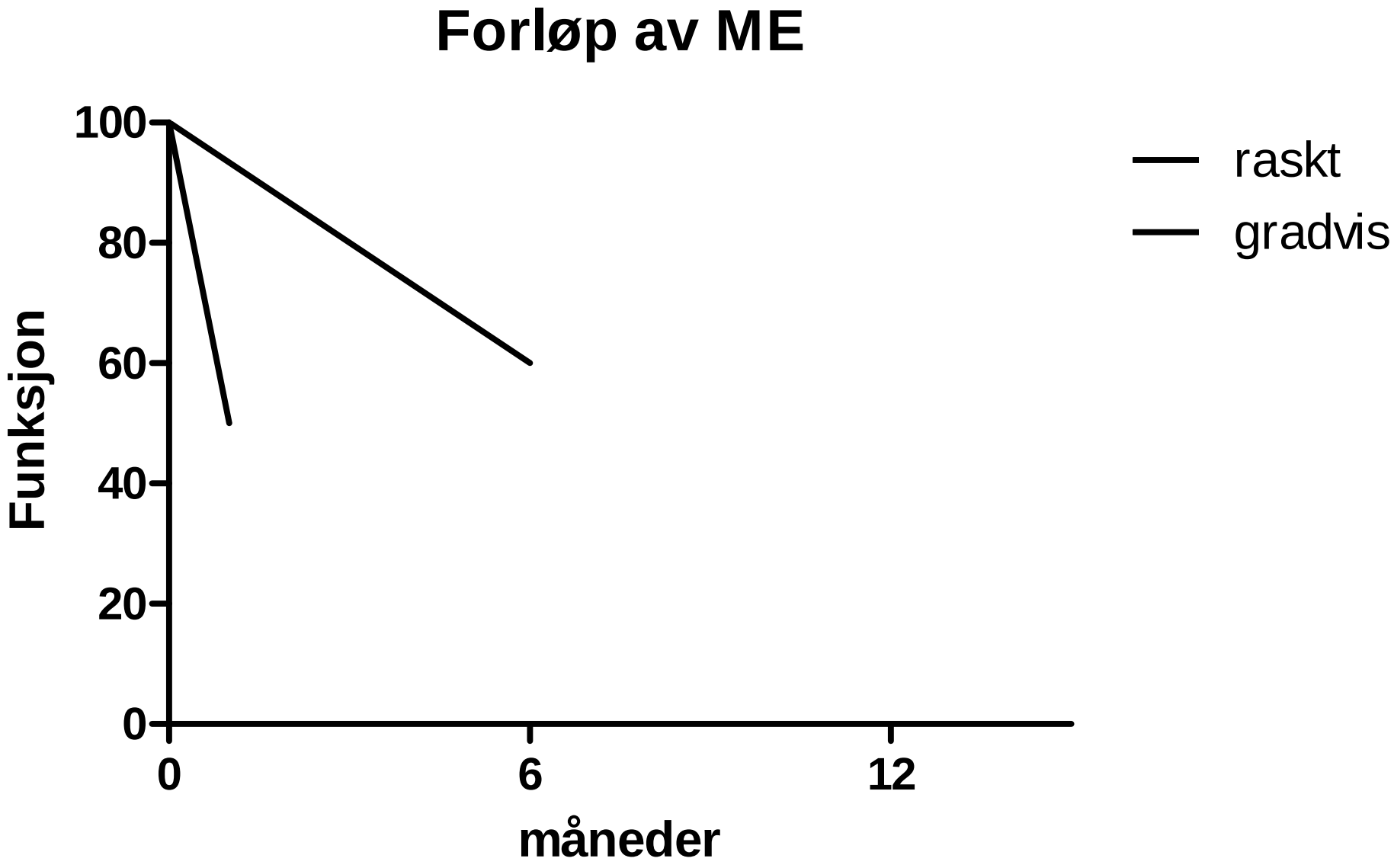
# Forløp av ME

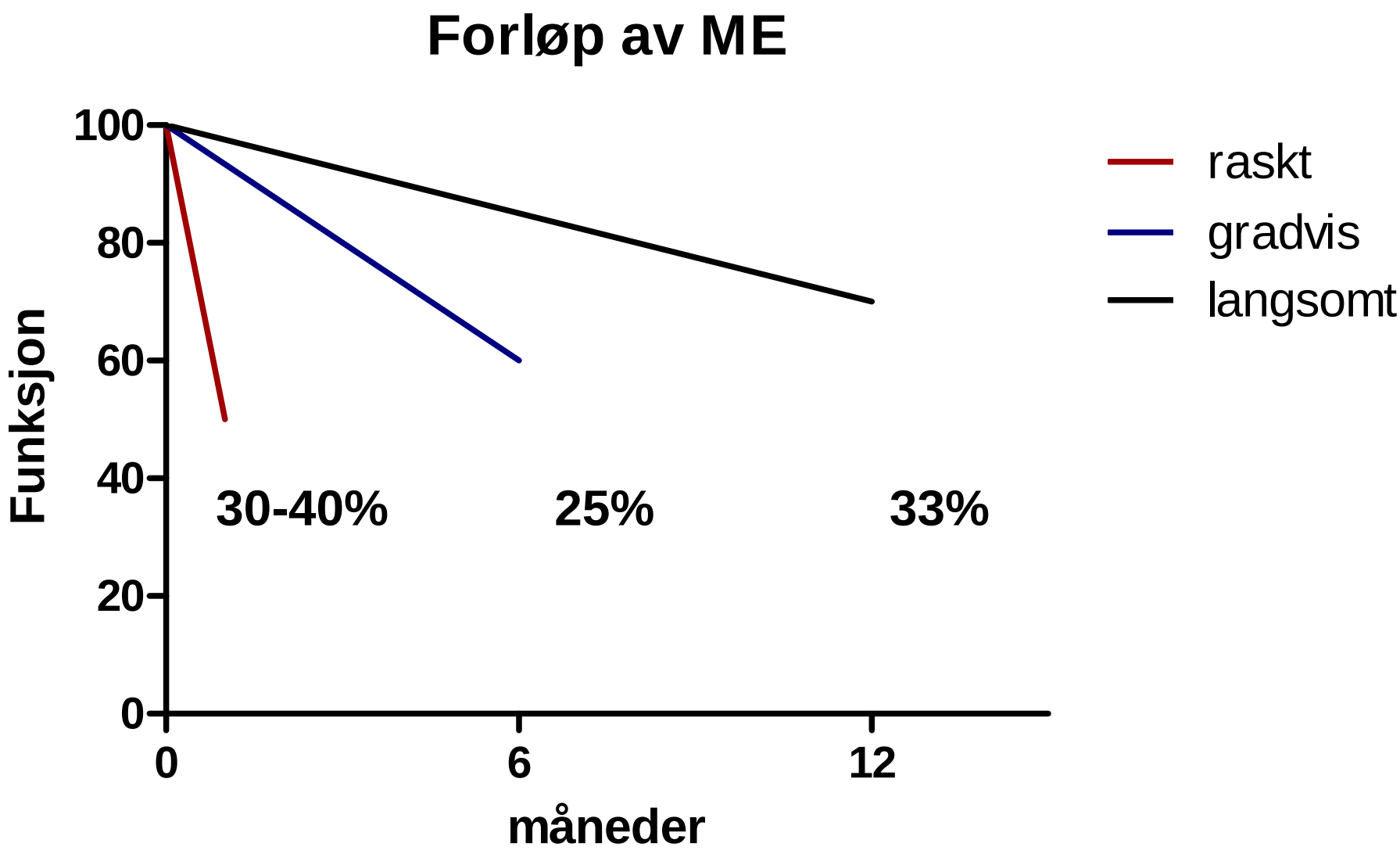
| | Husbundet | Ikke-Husbundet |
|---|---|---|
| Raskt < 1 måned | 42 | 33 % |
| Gradvis < 1 år | 22 | 28 % |
| Langsomt > 1 år | 32 | 37 % |

Pendergrast et al, 2016

# Forløp av ME



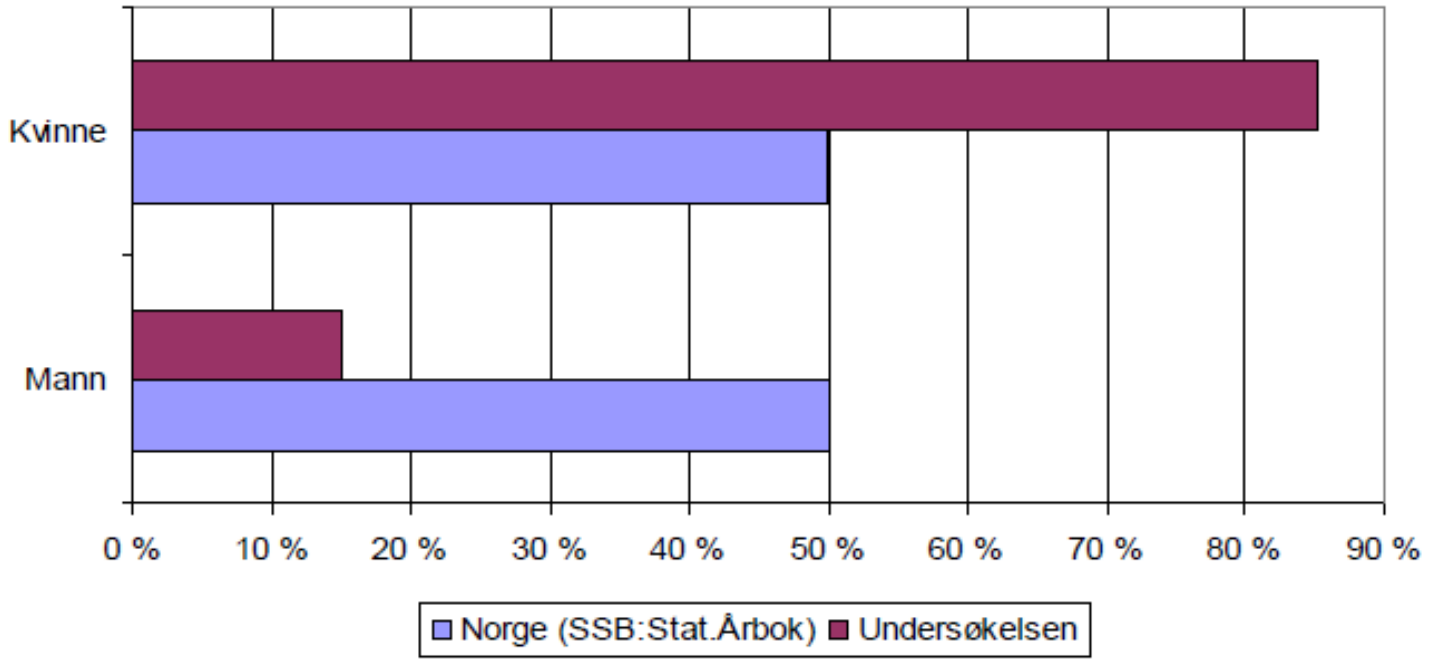

Forløp av ME
100
80
60
40
20
0
Funksjon
0
6
12
måneder
raskt
gradvis


Forløp av ME
100
80
60
40
20
0
Funksjon
30-40%
25%
33%
0
6
12
måneder
raskt
gradvis
langsomt

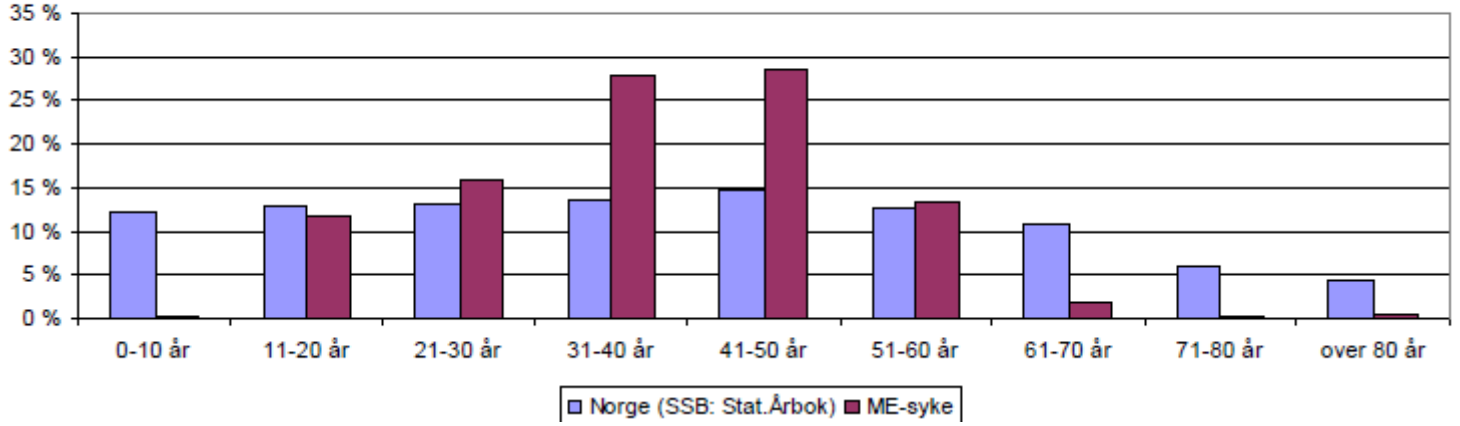
# Hyppighet og fordeling

2-4 per 1000?

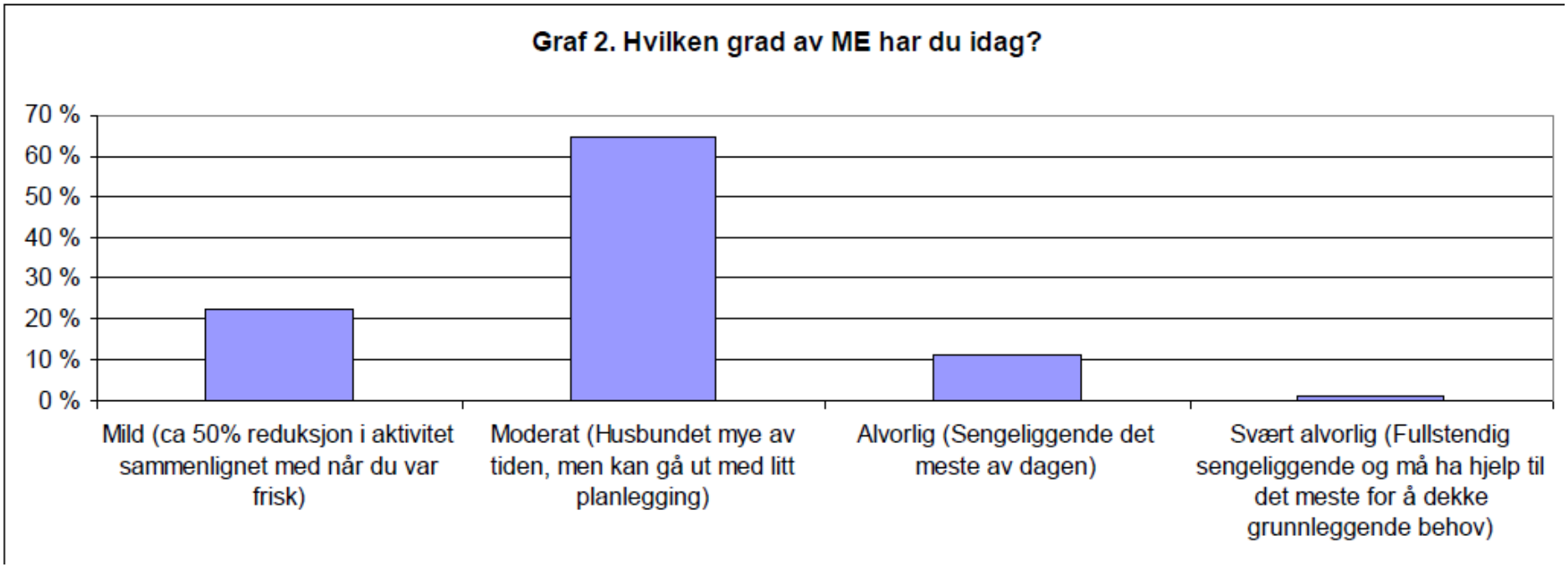
## Graf 21. Kjønn




## Graf 22. Hvor gammel er du?



# Fordeling av alvorlighetsgrad ved ME




| | |
|---|---|
| Mild | 1/4 |
| Moderat | 2/3 |
| Alvorlig | 1/7 |
| Svært alvorlig | 1/70 |

NORGES MYALGISK ENCEFALOPATI FORENING

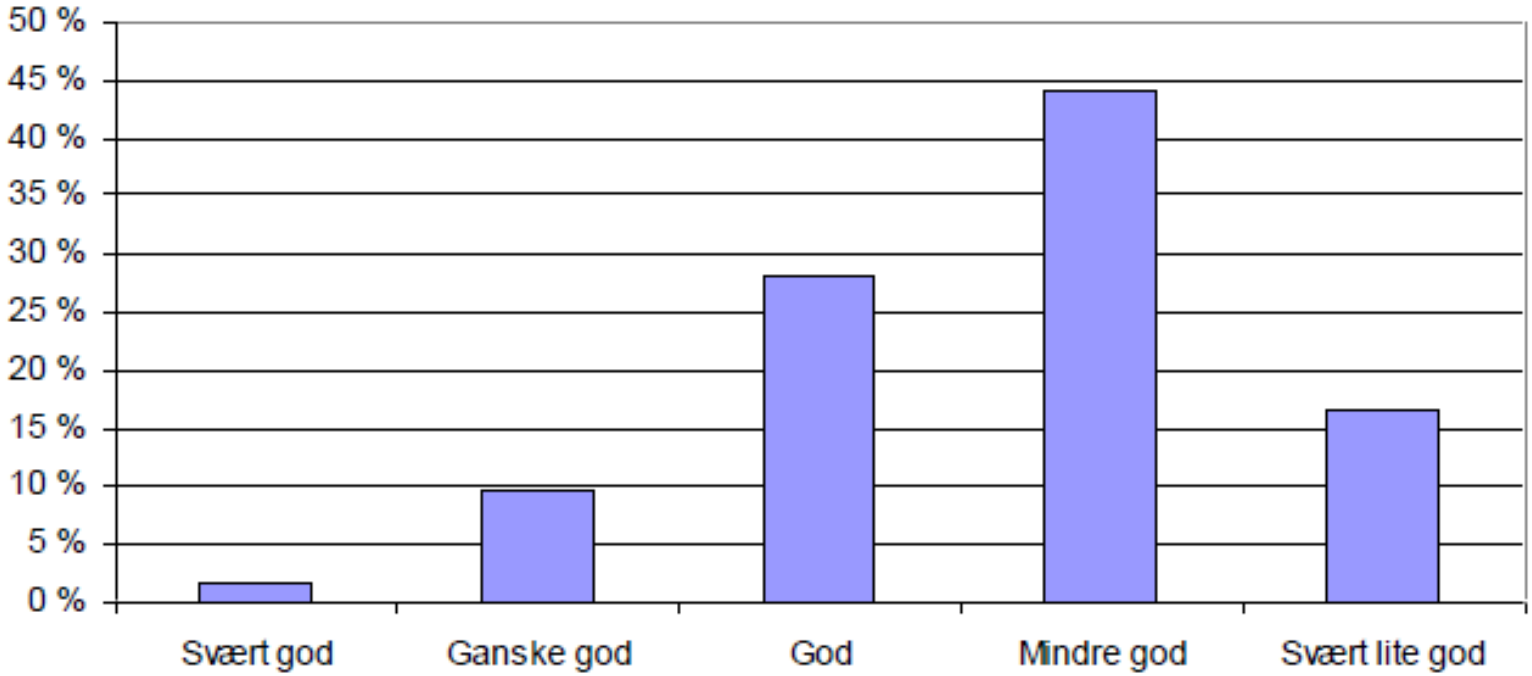
Gunn J. Bringsli, Anette Gilje og Bjørn K. Getz Wold

ME-SYKE I NORGE – FORTSATT BORTGJEMT?

Oslo, 12. mai 2013

# Livskvalitet - Egenvurdering

**Graf 20. Dersom du skal vurdere din livskvalitet for tiden. Vil du betegne den som**




NORGES MYALGISK ENCEFALOPATI FORENING

# Symptomer ved ME

Det Store Gjenombruddet!

Institute of Medicines Rapport Februar 2015

# Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness

## DETAILS

304 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-31689-7 | DOI 10.17226/19012

INSTITUTE OF MEDICINE
*OF THE NATIONAL ACADEMIES*

**Advising the Nation. Improving Health.**

# PEM:Post Extertional  Malaise
# Utmattelse/ubehag etter anstrengelse ved ME

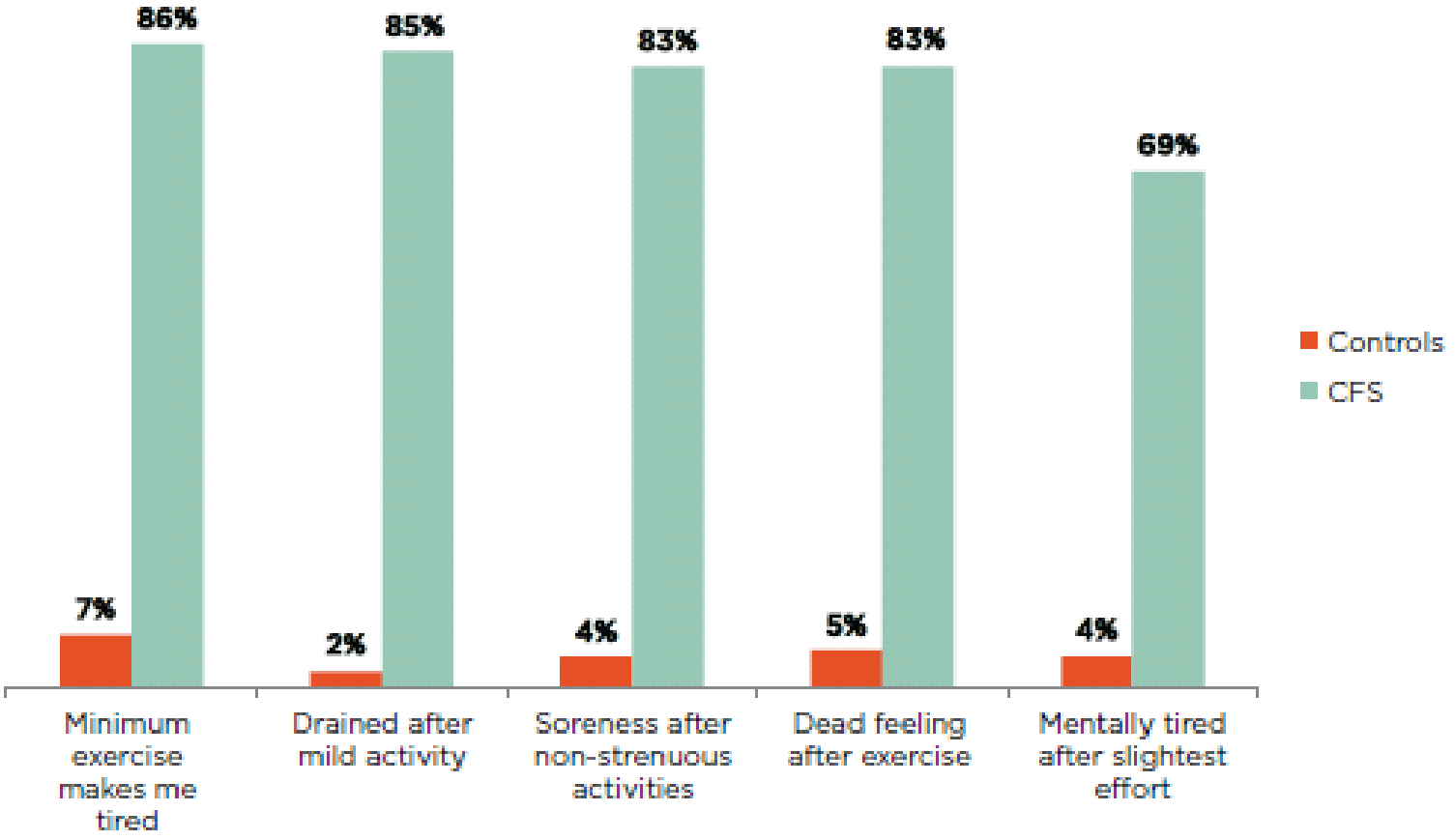



FIGURE 4-1 Percentage of ME/CFS patients and healthy controls reporting PEM symptoms of at least moderate severity that occurred at least half of the time during the past 6 months.
NOTE: All patients fulfilled the Fukuda definition for CFS.

# Kognitive problemer ved ME

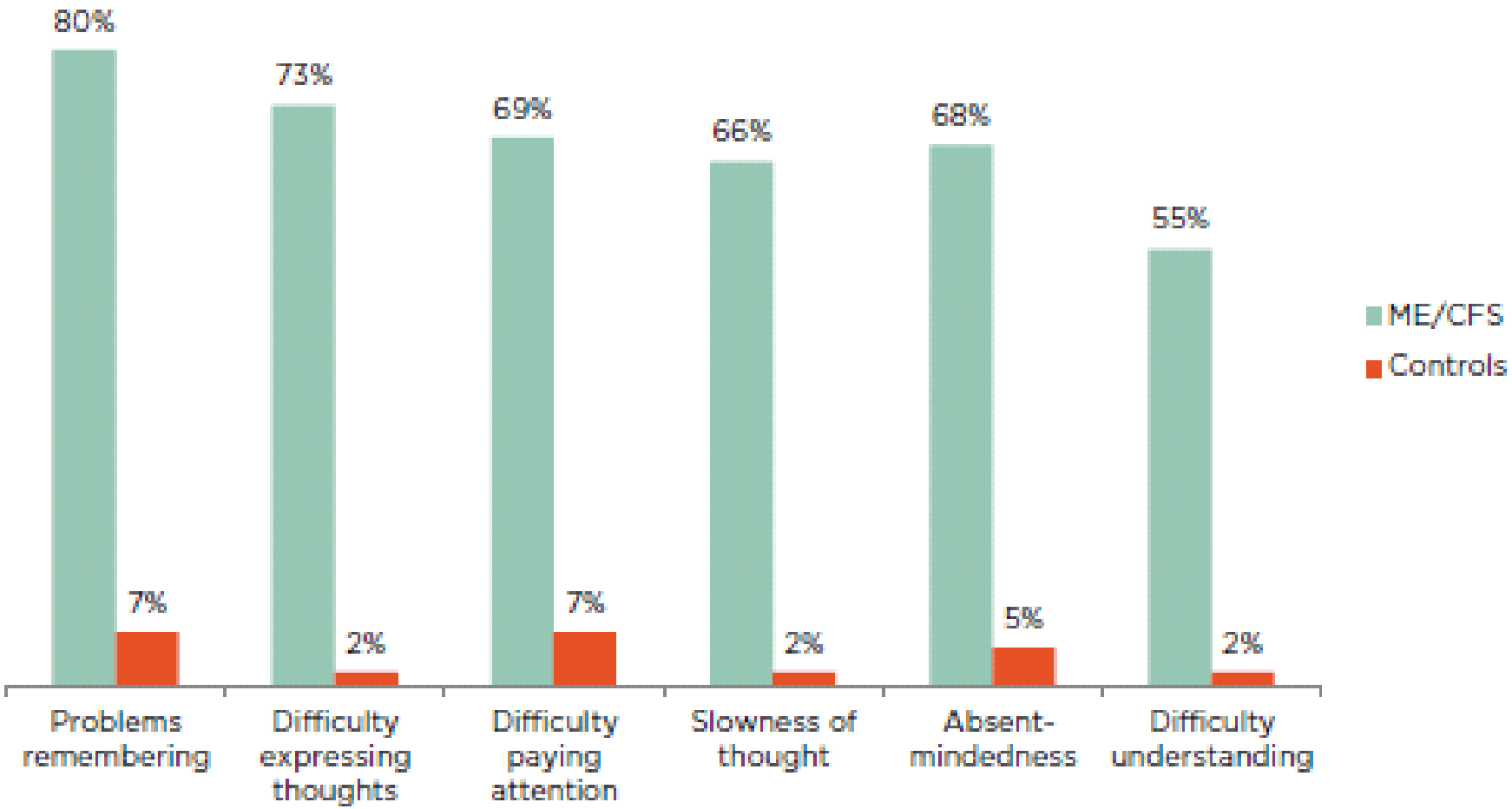



FIGURE 4-3 Percentage of ME/CFS patients and healthy controls reporting neurocognitive manifestations of at least moderate severity that occurred at least half of the time during the past 6 months.

# Smerter ved ME

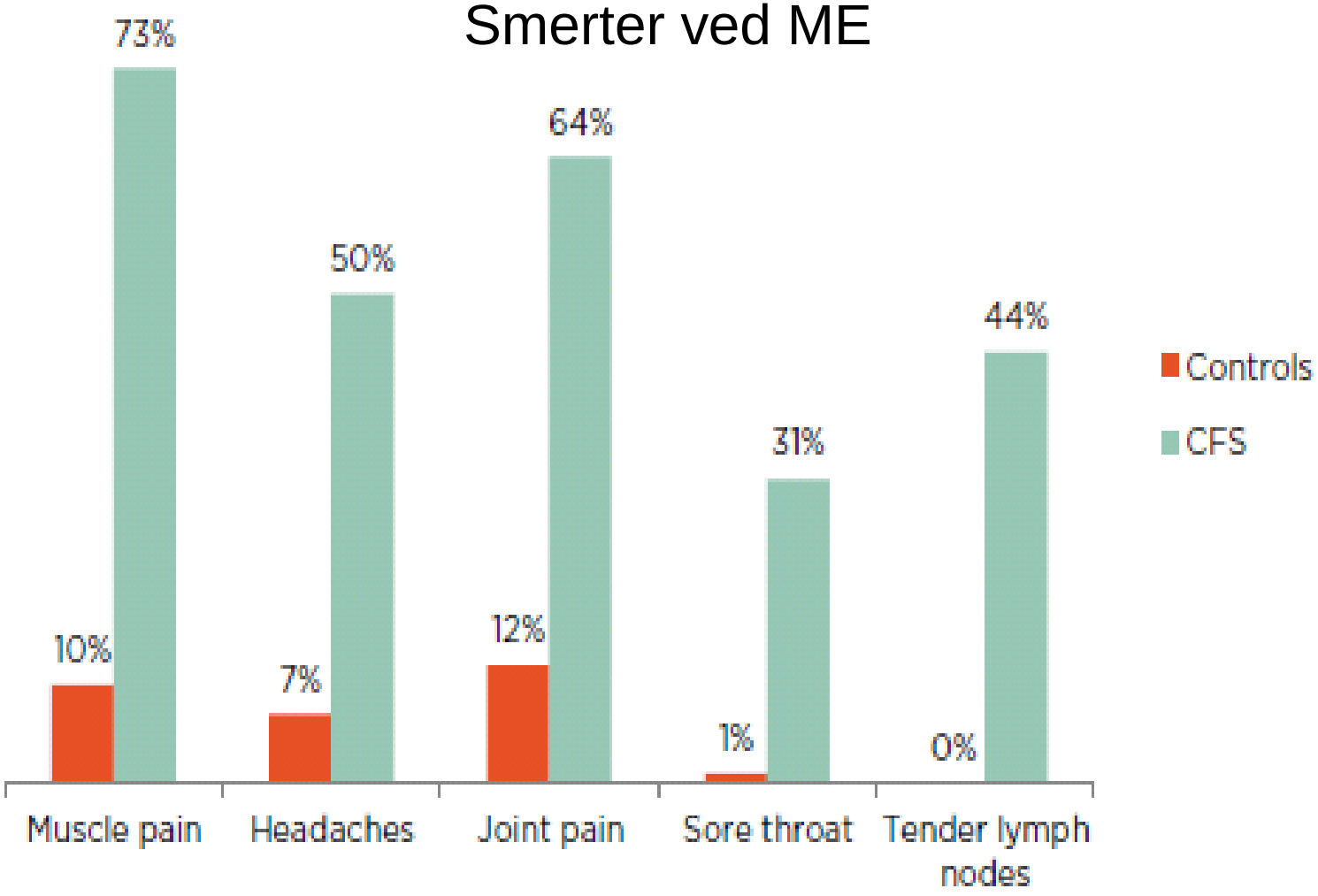



**FIGURE 5-1** Percentage of ME/CFS patients and healthy controls reporting pain symptoms of at least moderate severity that occurred at least half of the time for the past 6 months.
NOTE: All patients fulfilled the Fukuda definition for CFS.

# Søvnproblemer ved ME

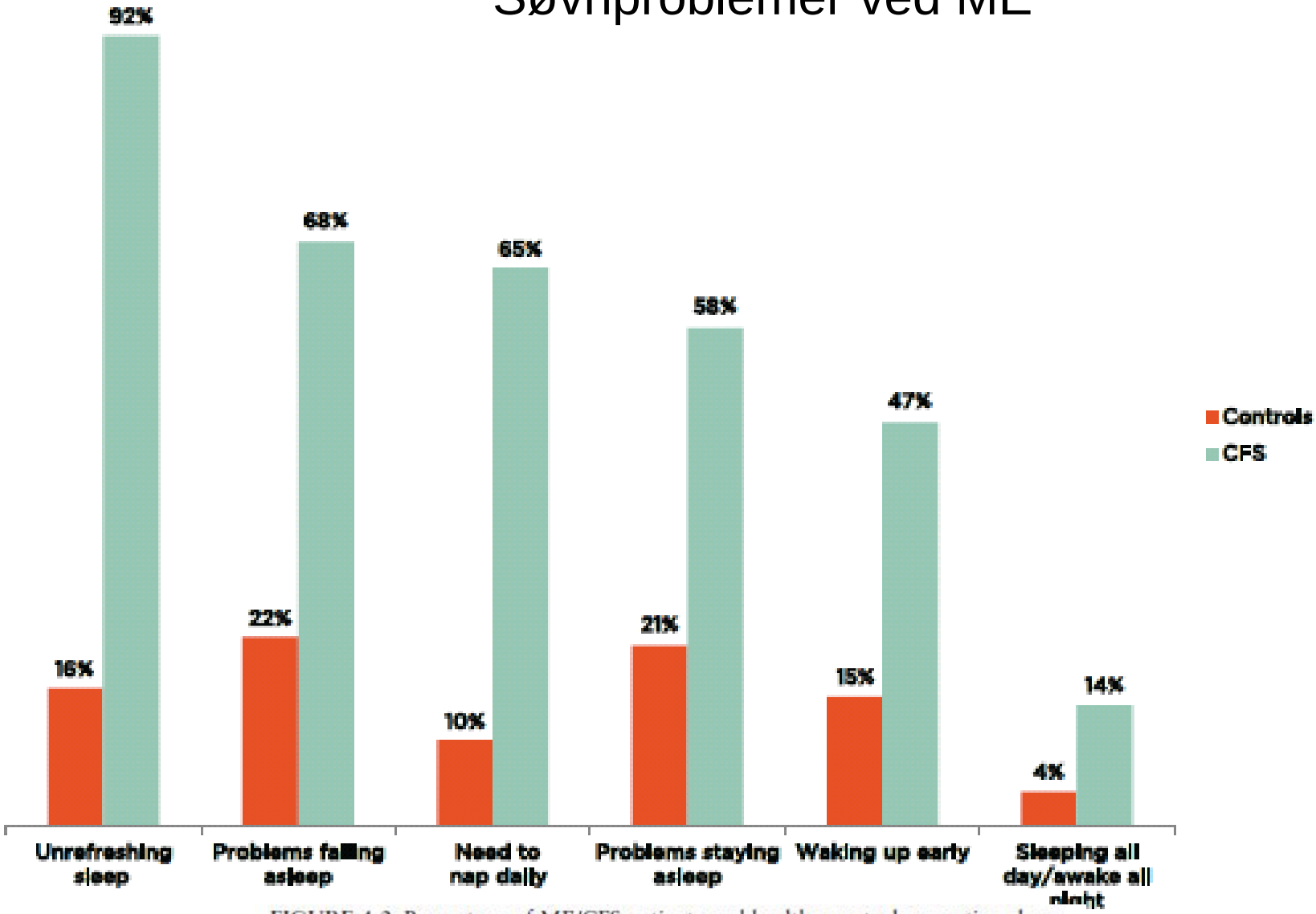



FIGURE 4-2 Percentage of ME/CFS patients and healthy controls reporting sleep-related symptoms of at least moderate severity that occurred at least half of the time during the past 6 months.
NOTE: All patients fulfilled the Fukuda definition for CFS.

# Immunrelaterte symptomer ved ME

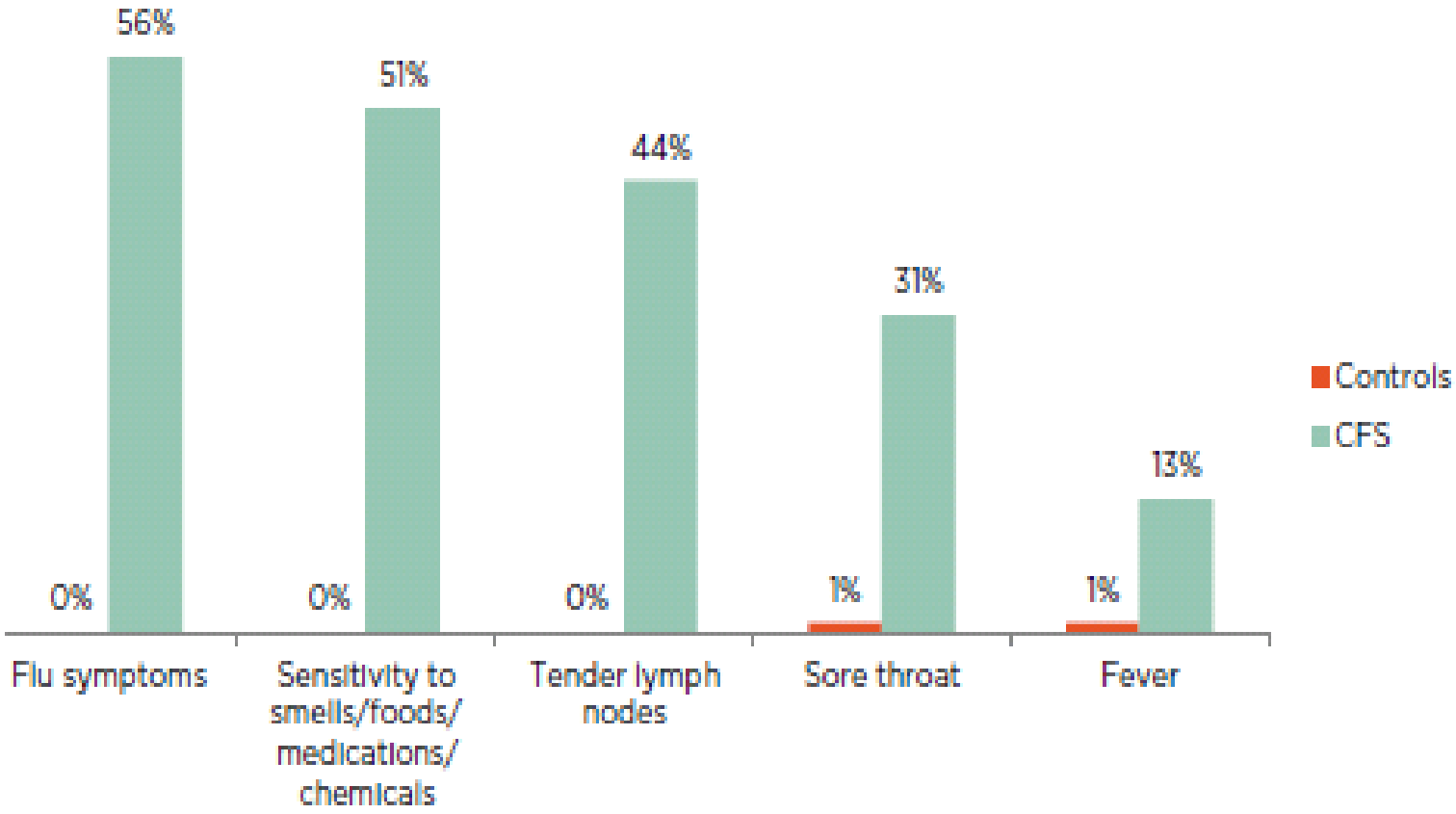



**FIGURE 5-2** Percentage of ME/CFS patients and healthy controls reporting immune-related symptoms of at least moderate severity that occurred at least half of the time for the past 6 months.
NOTE: All patients fulfilled the Fukuda definition for CFS.

# Neuroendokrine symptomer ved ME

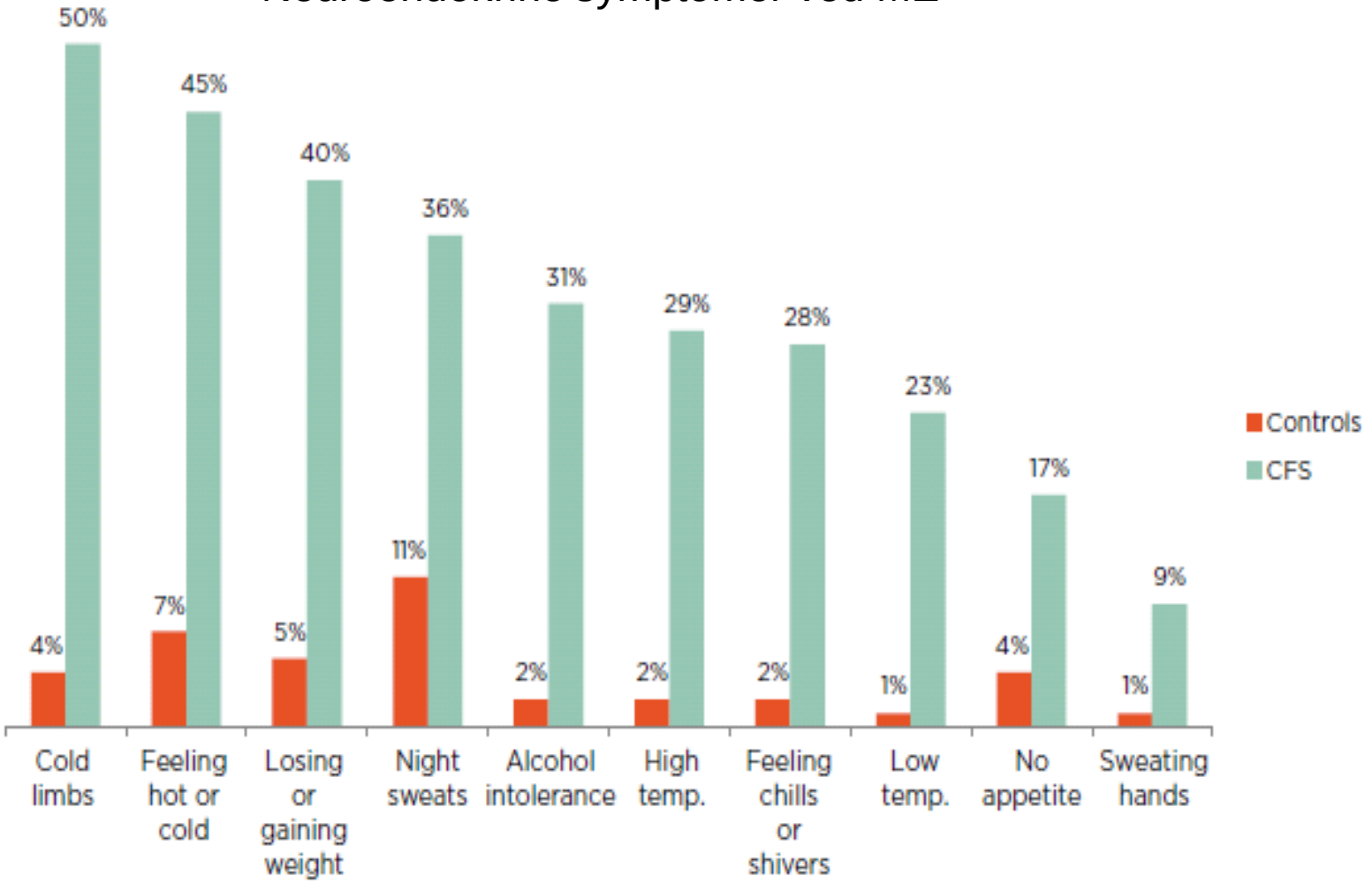



FIGURE 5-3 Percentage of ME/CFS patients and healthy controls reporting neu endocrine manifestations of at least moderate severity that occurred at least half the time for the past 6 months.
NOTE: All patients fulfilled the Fukuda definition for CFS.

# Oppsummering:
# Symptomer ved ME

- Utmattelse etter anstrengelse (PEM)
- Kognitive problemer
- Smerter
- Søvnproblemer ved ME
- Ortostatisk hypotensjon
- Immunrelaterte symptomer
- Neuroendokrine symptomer
- Mage- tarm problemer

# Behandling ved ME

# Hva bestemmer behandlingstilbudet ved ME?

# Behandlingstilbud ved ME

Man må kjenne:

- Diagnosen
- Årsak og utløsende årsak(er)
- Hyppighet
- Sykdomsforløpet
- Symptomer
- Behandlingsmuligheter


# Behandlingsmuligheter

**Gunn J. Bringsli, Anette Gilje og Bjørn K. Getz Wold**

NORGES MYALGISK ENCEFALOPATI FORENING

20% sier at de er blitt så dårlig behandlet på lokalt sykehus at de ikke lenger tør ta kontakt.

Bare 29% får jevnlig oppfølging fra fastlege.

**Gunn J. Bringsli, Anette Gilje og Bjørn K. Getz Wold**

# ME-SYKE I NORGE – FORTSATT BORTGJEMT?

**Oslo, 12. mai 2013**

# ME og Behandlingsapparatet

Fortsatt får pasienter beskjed om at de kan bli friske hvis de selv vil

- Helsevesenet
- NAV
- Barnevern

**Table 1. Overview of the included pharmacological interventions for CFS/ME**

| INTERVENTION (Study ID) | POPULATION CHARACTERISTICS AND CASE DEFINITION | | | OUTCOMES REPORTED | | Quality rating | Author (year) |
|---|---|---|---|---|---|---|---|
| | Study design | Participants Duration of follow-up | Case definition | Fatigue measures | Physical Functioning status | | |
| Rintatolimod (AMP-502) | Phase II RCT. i.v. rintatolimod vs. placebo | 92 patients 6 mo. | 1988 CDC/Holmes | Exercise duration: (p= 0.007) Exercise work: (p= 0.011) | KPS: p=0.023 ADL: p=0.034 SCL-90R: p= 0.05 | FAIR | (Strayer *et al.*, 1994) |
| Rintatolimod (AMP-516) | Phase III RCT. i.v. rintatolimod vs. placebo | 234 patients 10 mo. | 1998 CDC/Holmes | ET on a treadmill with ECG testing (p= 0.047) | KPS, ADLs, Vitality and SF-36 scores were measured pre-and post-tto, but not compared between groups | FAIR | (Strayer *et al.*, 2012) |
| Rituximab (Pilot study) | Case cohort, Open-label study. Infusions of RTX vs. placebo | 3 patients 10 mo. | 1994 CDC/Fukuda | NR | Improved physical health and function scores | FAIR | (Fluge *et al.*, 2009) |
| Rituximab (KTS-1-2008) | Small RCT phase II study. Infusions of RTX vs. placebo | 30 patients 12 mo. | 1994 CDC/Fukuda | Fatigue levels (p= 0.51) | Improved physical health and function scores | FAIR | (Fluge *et al.*, 2011) |
| Rituximab (KTS-2-2010) | Single-center open-label, one armed, no-randomized Phase II study. Infusions of RTX vs. placebo | 29 patients 15 mo treatment to 36 mo. | 1994 CDC/Fukuda | Fatigue score (at least 6-wks) Fatigue: 8 (6.3-10) Cognitive: 7.5 (4.7-10) Pain: 7.2 (4-9) ME/CFS overall: 8.2 (6-10) | Baseline function level: 15% (5-50) Baseline total SF-36 Physical health: 25.6 ± 6.6 Mental health: 44.6 ± 10.4 | FAIR | (Fluge *et al.*, 2015) |

Table contô

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Valganciclovir (EVOLVE) | RCT. Oral valganciclovir vs. placebo | 30 patients 48 wk. 6 mo. tto and 6 more mo. follow-up (unbinding and outcomes measured at 9 mo.) | 1994 CDC/Fukuda | Change at 9 mo. for MFI-20: p= 0.224 and FFS: p= 0.006 | Physical function: p= 0.217 Cognitive functioning: p= 0.025 | FAIR | (Montoya *et al.*, 2013) |
| Hydrocortisone + Fludrocortisone | Crossover RCT. Oral hydrocortisone + fludrocortisone vs. placebo | 80 patients 6 mo. | 1994 CDC/Fukuda | VAS score (0-10) Fatigue degree: p= 0.76 AFQ score (4-28): p= 0.69 | SF-36 physical score: p= 0.34 SF-36 mental score: p= 0.02 | FAIR | (Blockmans *et al.*, 2003) |
| Hydrocortisone | RCT, single center. Oral hydrocortisone vs. placebo | 65 patients 3 mo. | 1988 CDC/Holmes | Mean changes POMS subscales Fatigue : p= 0.21 VIGOR: p= 0.45 | Mean changes Activity scale: p= 0.32 Global wellness score: p< 0.001 | FAIR | (McKenzie *et al.*, 1998) |
| Immunoglobulins | RCT. i.v. IgG vs. placebo | 30 patients 6 mo. follow-up | 1988 CDC/Holmes | NR | MOS-SF-12 (0-100 score) Physical subscale, mental health and social functions: all p= NS Health perception: p< 0.05 | FAIR | (Peterson *et al.*, 1998) |
| Isoprinosine (Immunovir) | RCT. Oral isoprinosine tablets vs. placebo | 16 patients 3 mo. tto to 7 mo. follow-up | 1988 CDC/Holmes and 1994 CDC/Fukuda | NR | SCL-90R: p= 0.25 KPS: p= 0.46 ADL: data not provide | POOR | (Diaz-Mitoma F, 2003) |

*Castro-Marrero J et al in press*

Table contô

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Acetyl-L-carnitine vs. Propionyl-L-carnitine vs. combination | Exploratory, open-label RCT. Oral ALC vs. PLC vs. placebo | 90 patients 6 mo. | 1994 CDC/Fukuda | MFI-20 (4-20 score) General fatigue (at 4 mo.): p= 0.0003 Physical fatigue (at 4 mo.): p= 0.007 Mental fatigue (at 4 mo.): p= 0.010 General fatigue (at 6 mo.): p= 0.004 Physical fatigue (at 6 mo.): p= 0.009 Mental fatigue (at 6 mo.): p= 0.015 | NR | FAIR | (Vermeulen *et al.*, 2004) |
| Essential fatty acids | RCT Oral linolenic acid, gamma-linolenic acid, EPA and DHA vs. placebo | 63 patients 3 mo. | 1991Oxford criteria for PVFS | Self reported fatigue (0-3) At 1 mo.: p=:0.09 At 3 mo.: p= 0.0003 | Physical symptom: p= NS | FAIR | (Behan *et al.*, 1990) |
| Behan's replication study | RCT Oral Efamol marine vs. placebo | 50 patients 3 mo. | 1991 Oxford | Self reported fatigue (0-3) At 1 and 3 mo.: all p= NS | Physical symptom: p= NS | FAIR | (Warren *et al.*, 1999) |
| Magnesium | RCT i.m. 50% magnesium sulfate injections vs. placebo | 32 patients (non magnesium deficiency 1.5 mo. follow-up | 1990 Australian definition | Mean change in NHPES (at 1.5 mo.): p= 0.002 | Pain: p= 0.011 Emotional reaction: p= 0.013 Overall NHPES: p= 0.001 | FAIR | (Cox *et al.*, 1991) |
| Vitamin $B_{12}$ | Crossover RCT i.m. injections of hydroxocobalamin vs. placebo | 29 patients 1.5 mo. | General practitioners and hospital staff inquiry on tiredness and fatigue | Fatigue level: p= 0.09 | Rating general well-being: p= 0.006 Rating happiness: p= 0.032 | FAIR | (Ellis *et al.*, 1973) |

Table contô

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vitamin $B_{12}$ | Crossover RCT. i.m. injections of a liver extract-folic acid cyanocobalamin (LEFAC) combination vs. placebo | 15 patients Follow-up NR | 1988 CDC/Holmes | p= NS | p= NS | POOR | (Kaslow *et al.*, 1989) |
| Vitamin $B_{12}$ | Case report. High dose of i.m. Vitamin B12 injections twice weekly | 2 women with CFS Follow-up NR | 1998 CDC/Holmes | Self-reported energy p= NS | NR | FAIR | (Wiebe, 1996) |
| Vitamin $B_{12}$ plus folic acid | Cross-sectional survey. i.m. cyanocobalamin injections plus oral folic acid | 38 female patients Follow-up NR | 1994 CDC/Fukuda and 2003 Canadian criteria (40% fulfilled 1990 FMS criteria) | NR | FFS score (0–6): p= NS PGIC score (1-7): p< 0.0005 | FAIR | (Regland *et al.*, 2015) |
| NADH (ENADA study) | Cross-over RCT. Oral NADH vs. placebo | 26 patients 3 mo. | 1994 CDC/Fukuda | NR | NR | FAIR | (Forsyth *et al.*, 1999) |
| NADH | RCT Oral NADH or nutritional supplements vs. psychotherapy | 31 patients 24 mo. | 1994 CDC/Fukuda | Symptoms score at 3 mo.: p= 0.001 at 6, 12 and 24 mo.: p= NS | NR | FAIR | (Santaella *et al.*, 2004) |
| NADH (VitaNADH) | RCT Oral NADH vs. placebo | 77 patients 3 mo. | 1994 CDC/Fukuda | p= NS | Reduction in self-reported symptoms by HADS Anxiety: p< 0.05 Depression: p=NS | FAIR | (Alegre *et al.*, 2010) |
| $CoQ_{10}$ + NADH (ReConnect) | A proof of concept RCT. Oral $CoQ_{10}$ plus NADH vs. placebo | 80 patients 2 mo. | 1994 CDC/Fukuda | Total FIS 40 score Baseline:p= 0.32 1 mo.: p= 0.71 2 mo.: p= 0.03 | Self-report outcomes for pain and sleep 1 mo.: p= NS 2 mo.: p= NS | GOOD | (Castro-Marrero *et al.*, 2016) |



*Castro-Marrero J et al in press*

Immunglobulin ved ME er det effektivt?

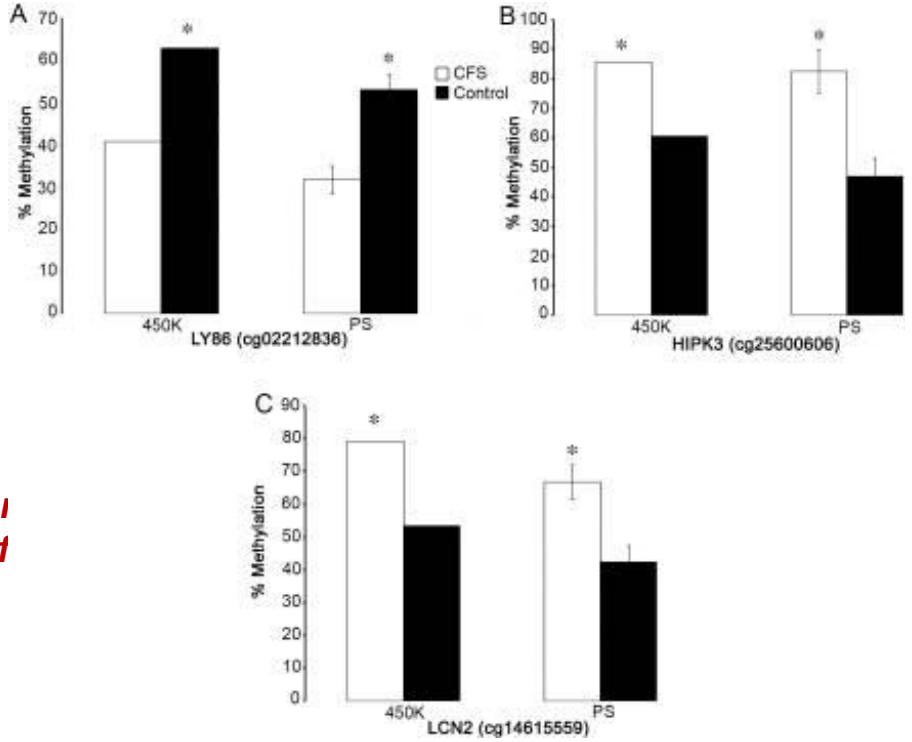
Intravenous Immunoglobulin is ineffective in the treatment of patients with Chronic fatigue syndrome
*Vollmer-Conna U et al American J of Medicine 1997;103:38-43*

Successful Intravenous Immunoglobulin therapy in 3 cases of Parvovirus B19-associated Chronic Fatigue syndrome
*Kerrr JR et al Clinical Infectious Diseases 2003;36:e100.6*

# B12 vitamin og ME

## B-12 er en antioxidant og en methyldonor

Hypomethylering er blitt påvist ved ME




*Genes associated with immune cell regulation, the largest coordinated enrichment of differentially methylated pathways, showed hypomethylation within promoters and other gene regulatory elements in CFS.*
***These data are consistent with evidence of multisyste dysregulation in CFS and implicate the involvement o DNA modifications in CFS pathology***

*Birch CS et al Free Radic Biol Med 2009;47:184-8*
*De Vega WC et al Plos One 2014;9:e104757*

# B12 vitamin og ME

38 ME pasienter hadde fått B-12
15 var gode respondere og 23 «mild» respondere

De gode respondere hadde brukt høyere og hyppigere doser over tid og brukte høyere Folsyredoser.
Det er viktig å korrigere evt skjoldbrukskjertel svikt for å få en god respons

Methylcobolamin er mer effektivt en hydroxycobalamin. Injeksjon mer effektivt enn per oralt, varighet fra 6mnd til 20 år

Injeksjon i gjn.sn hver 4 dag (god respons) vs 6 dager (mild respons)

Regland B et al Plos One 2015; 10:e0124648

| Variables | Good responders | Mild responders | p-value |
|---|---|---|---|
| Age (years) | 51.6 ± 11.2 | 46.8 ± 8.9 | *n.s.* |
| Duration of illness (years) | 16.6 ± 5.7 | 13.5 ± 9.7 | *n.s.* |
| Global Impression of change (pts) | 2.7 ± 0.5 | 1.8 ± 0.6 | < 0.0005 |
| Duration of B12 injections (years) | 8.1 ± 6.4 | 2.2 ± 2.3 | < 0.0005 |
| Interval days between B12 inj. | 3.8 ± 1.9 | 5.8 ± 1.7 | < 0.03 |
| Folic acid mg/day | 6.7 ± 6.6 | 1.9 ± 2.0 | < 0.003 |
| Use of high-concentrated B12 | 14/15 = 93% | 13/23 = 57% | < 0.03 |
| MTHFR compound heterozygote | 1/15 = 7% | 8/23 = 35% | *n.s.* (< 0.07) |
| Daily use of Thyroid hormone | 7/15 = 47% | 2/23 = 9% | < 0.02 |
| Daily use of prescribed analgesic | 0/15 = 0% | 16/23 = 70% | < 0.0005 |
| Fibromyalgia as part of ME | 3/15 = 20% | 12/23 = 52% | *n.s.* (< 0.09) |

Mean ± SD or frequency/percentage for a number of variables in Good (n = 15) or Mild responders (n = 23). P-value is calculated by Student's t-test, or by Fischer's exact two-tailed test in the categorical data. (n.s. = no significance)

doi:10.1371/journal.pone.0124648.t002

Regland B et al Plos One 2015; 10:e0124648

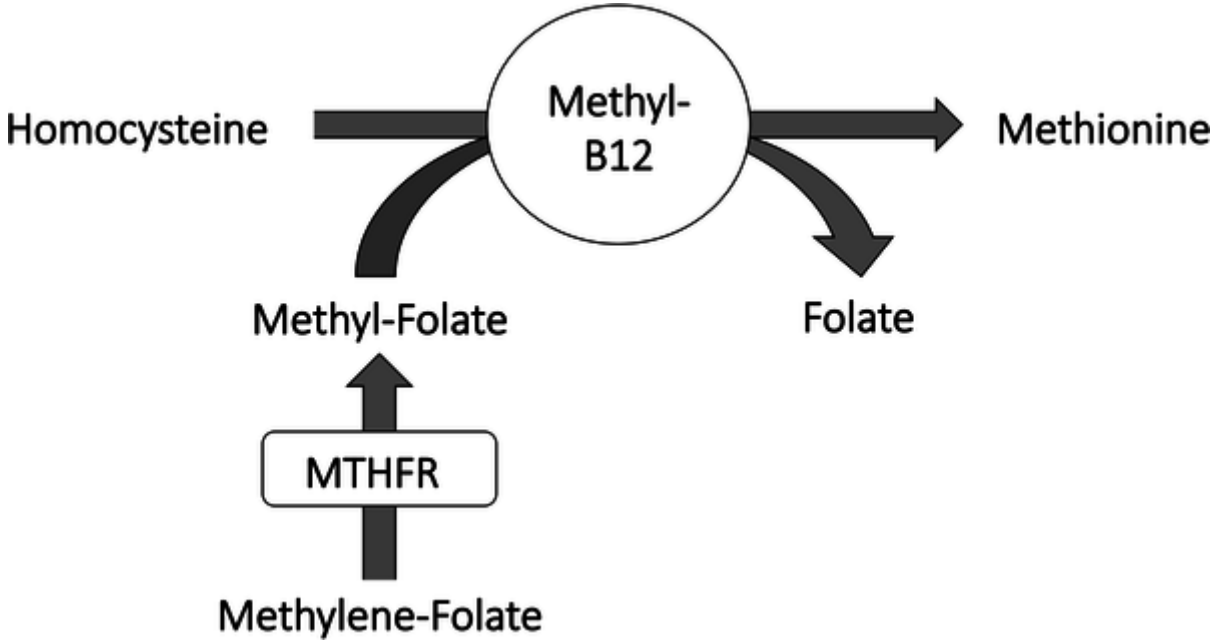
| Patient group | Tramadol | Codeine | Buprenorhine | Duloxetine | Pregabalin |
|---|---|---|---|---|---|
| Good responders n = 15 | 0 | 0 | 0 | 0 | 0 |
| Mild responders n = 23 | 5 | 2 | 2 | 4 | 4 |

Number of Good and Mild responders on daily use of prescribed analgesics. Tramadol, Codeine and Buprenorphine are opioids, while Duloxetine and Pregabalin are approved for the management of neuropathic pain. One patient was using Tramadol and Duloxetine at the same time.

doi:10.1371/journal.pone.0124648.t003

Regland B et al Plos One 2015; 10:e0124648

# B-12 og Folsyre ved ME




Frequent injections of high-concentrated vitamin B12, combined with an individual daily dose of oral folic acid, may provide blood saturations high enough to be a remedy for good and safe relief in a subgroup of patients with ME/FM.

Moreover, we suspect a counteracting interference between B12/folic acid and certain opioid analgesics and other drugs which have to be demethylated as part of their metabolism.

Furthermore, it is important to be alert on co-existing thyroid dysfunction. These issues should be considered when controlled trials for ME and fibromyalgia are to be designed.

*Regland B et al Plos One 2015; 10:e0124648*

**Table 2. Overview of the included non-pharmacological interventions for CFS/ME**

| INTERVENTION (Study ID) | POPULATION CHARACTERISTICS AND CASE DEFINITION | | | OUTCOMES REPORTED | | Quality rating | Author (year) |
|---|---|---|---|---|---|---|---|
| | Study design | Participants Duration of follow-up | Case definition | Fatigue measures | Physical Functioning status | | |
| CBT | RCT<br>CBT vs. usual care for symptoms | 30 patients<br>12 mo. | 1991 Oxford | NR | KPS score of ≥ 80<br>At 5 mo. 27%<br>At 8 mo.: 53%<br>At 12 mo.: 73%<br><br>Improvement ≥ 10 point on KPS<br>At 5 mo. 23%<br>At 8 mo.: 60%<br>At 12 mo.: 73% | GOOD | (Sharpe *et al.*, 2015) |
| CBT | RCT<br>CBT vs. control for symptoms | 69 patients<br>3 mo. | 1994 CDC/Fukuda | Fatigue subscale (0-28 scoring)<br>At 3 mo.: p= 0.06 | NR | FAIR | (Lopez *et al.*, 2011) |
| Counseling therapy | RCT<br>Counseling vs. wait list for symptoms | 47 patients<br>12 mo. | 1994 CDC/Fukuda | NR | NR | GOOD | (Jason *et al.*, 2005) |
| Self-instruction therapy | RCT<br>Self-instruction therapy vs. wait list for symptoms | 169 patients<br>6-12 mo. depending on tto duration | 1994 CDC/Fukuda | CIS fatigue severity scores (8-56)<br>Second assessment: p< 0.001<br>CIS fatigue severity scores (CIS <35 and reliable change index of >1.96): p< 0.001 | SF-36 PF scale<br>Second assessment: p= 0.011<br><br>Functional impairment SIP-8 scores<br>Second assessment: p< 0.001 | FAIR | (Knoop *et al.*, 2008) |

*Castro-Marrero J et al in press*

Table 2 contô

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Stepped care therapy | RCT<br>Stepped care vs. usual care for symptoms | 169 patients<br>6-12 mo. depending on treatment duration | 1994 CDC/Fukuda | CIS fatigue severity scores<br>Post-tto: p= 0.92<br>CIS fatigue severity scores (CIS <35 and reliable change index of >1.96): p= 1.00 | SF-36 PF scale<br>Post-tto: p= 0.72<br><br>Functional impairment<br>SIP-8 scores<br>Post-tto: p= 0.77 | GOOD | (Tummers *et al.*, 2010) |
| CBT | Non-RCT<br>CBT vs. wait list for symptoms | 65 patients<br>6 mo. | 1994 CDC/Fukuda | CIS fatigue severity scores at 6 mo: p=0.099 | Functional impairment<br>SIP-8 scores at 6 mo.:<br>p= NS<br>Change from baseline:<br>p= 0.004 | FAIR | (Bazelmans *et al.*, 2005) |
| CBT and support group | RCT<br>CBT vs. support group vs. usual care for symptoms | 153 patients.<br>12 mo. | 1994 CDC/Fukuda | CFQ-11 scale<br>6 mo.: p= 0.19<br>12 mo.: p= 0.19<br>Difference between groups from baseline at 12 months<br>CBT vs. support:<br>p= 0.011<br>CBT vs. usual care:<br>p= 0.027<br>Support vs. usual care:<br>p= NR | SF-36 PF scale<br>(all p= N.S. both at 6 and 12 mo.)<br><br>Difference between groups from baseline to 12 mo.<br>CBT vs. support:<br>p= 0.0055<br>CBT vs. usual care:<br>p= 0.0055<br>Support vs. usual care:<br>p= 0.15 | FAIR | (White *et al.*, 2011) |



*Castro-Marrero J et al in press*

Table 2 contô

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| FINE trial | RCT<br>Pragmatic rehabilitation vs. supportive listening vs. usual care for symptoms | 296 patients<br>5 mo. treatment;<br>17.5 mo. follow-up | 1991 Oxford | CFQ-11 scale scores<br>Treatment effect estimate at 5 mo.: p=0.021<br>Pragmatic rehab vs. usual care.<br>At 17.5 mo.: p= N.S.<br>CFQ-11 scale scores<br>At 5 mo.: 22.78 ± 8.56 vs. 26.27 ± 7.68<br>At 17.5 mo.: 23.90 ± 8.34 vs. 26.02 ± 7.11<br>Baseline HADS depression score: p= 0.022<br>Baseline HADS total score: p=0.039<br>EQ-5D self-care scale, those with severe problems: p <0.001<br>CFQ-11 scale scores (pragmatic rehab. vs. usual care)<br>Age: p= 0.044<br>Illness duration: p= 0.008<br>EQ-5D mobility scale; those with severe problems: p= 0.024 | SF-36 PF scale<br><br>Treatment effect estimate for supportive listening vs. usual care p= 0.035<br><br>At 17.5 mo.<br>p= N.S. | GOOD | (Wearden *et al.*, 2010)<br><br>(Wearden *et al.*, 2012)<br><br>(Wearden *et al.*, 2013) |
| GET | RCT<br>GET + fluoxetine vs. GET alone vs. fluoxetine alone vs. control for symptoms | 136 patients<br>6.5 mo. | 1991 Oxford | CFQ-11 scores < 4<br>% non-cases of fatigue<br>3 mo.: p= NS<br>6.5 mo.: p= 0.025<br>Exercise improved fatigue scale scores<br>3 mo.: p= 0.13<br>6.5 mo.: p= 0.07 | Functional work capacity<br>3 mo.: p= NR<br>6.5 mo: p= NR<br>Effect of exercise on functional work capacity<br>3 mo.: p= 0.005 | FAIR | (Wearden *et al.*, 1998) |
| GET | RCT<br>Graded exercise vs. standard medical care for symptoms | 49 patients<br>3 mo. treatment<br>Up to 6 mo. follow-up | 1994 CDC/Fukuda | CFQ-11 total fatigue scores<br>At 3 mo.: p= 0.02<br>CFQ-11 physical fatigue subscale scores<br>At 3 mo.: p= 0.02<br>CFQ-11 mental fatigue subscale scores<br>At 3 mo.: p= 0.03 | SF-36 PF subscale score at 3 mo.<br>p= 0.49 | FAIR | (Moss-Morris *et al.*, 2005) |
| Orthostatic training | RCT<br>Orthostatic training vs. placebo for symptoms | 38 patients<br>6 mo. treatment<br>Up to 12 mo. follow up | 1994 CDC/Fukuda | Improvement of ≥10 points on FIQ at 6 mo.: p= NR | Mean change in blood pressure drop with active stand at 6 mo. | FAIR | (Sutcliffe *et al.*, 2010) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CBT | RCT<br>CBT vs. COG vs. ACT vs. relaxation for symptoms | n° cases: NR<br>12 mo. follow-up | CFS questionnaire, psychiatric assessment for DSM-IV diagnosis, and medical assessment. | FSS scores<br><br>At 12 mo.: p= NR<br>Jason, 2009 data: (comparison by energy envelope)<br>Stayed within envelope vs. outside envelope<br>At 6 months: p= NR<br>At 12 months: p= NS<br>Change at 12 months from baseline: p< 0.01<br><br>Hlavaty, 2011 data: (comparison by homework compliance level)<br>Minimum vs. moderate vs. maximum<br>Change in score at 12 mo. from baseline: p= NR | SF-36 PF scores<br><br>At 12 mo.: p< 0.01 (CBT and COG over time vs. ACT over time)<br>% achieving clinically significant improvement: p= NS<br><br>Jason, 2009 data: (comparison by energy envelope)<br>Stayed within envelope vs. outside envelope<br>6 mo.: p= NR<br>12 months: p= NS<br>Change at 12 months from baseline: p=0.03<br><br>Hlavaty, 2011 data: (comparison by homework compliance level)<br>Minimum vs. moderate vs. maximum<br>Change in score at 12 mo. from baseline: p= NR | FAIR | (Jason *et al.*, 2009)<br><br>(Hlavaty *et al.*, 2011) |
| CBT plus GET | RCT<br>CBT + GET vs. usual care for symptoms | 115 patients<br>12 mo. | 1994 CDC/Fukuda | FIQ (0-160 score) at 12 mo.: p= N.S. | SF-36 PF (0-100 score) at 12 mo.: p= N.S. | FAIR | (Nunez *et al.*, 2011) |
| PACE trial | RCT<br>CBT vs. GET vs. APT vs. usual care for symptoms | 640 patients<br>13 mo. | 1991 Oxford | CFQ-11 scale scores (0-33) at 13 mo.<br><br>Mean difference from control: p= N.S vs. p= 0.0001 vs. p= 0.0003 vs. p= NR<br><br>Mean difference from APT: NR vs. p= 0.0027 vs. p= 0.0059 vs. NR<br><br>% improved from baseline (≥ 2 points): 65% vs. 76% vs. 80% vs. 65%<br><br>% within normal range (score ≤ 18): 22% vs. 41% vs. 33% vs. 21% | SF-36 PF scores (0-100) at 13 mo.<br><br>Mean difference from control: p=NS vs. p= 0.0068 vs. p= 0.0005 vs. NR<br><br>Mean difference from APT: NR vs. p= 0.0002 vs. p< 0.0001 vs. NR<br><br>% improved from baseline (by ≥ 8 points): 49% vs. 71% vs. 70% vs. 58%<br><br>% within normal range (score ≥ 60): 35% vs. 52% vs. 53% vs. 41% | GOOD | (White *et al.*, 2011)<br><br>(White *et al.*, 2013)<br><br>(Dougall *et al.*, 2014) |

# PACE studien

Sammenlignet:

- Gradert treningsterapi (GET) *lett trening 5 ganger i uken*
- Kognitiv adferdsterapi (CBT) *unngå frykt og redsel for aktivitet*
- Pacing - Aktivitetstilpasning *70% av den energien man har*
- Spesialist behandling *legekonsultasjon, råd, medikamenter*

*Oppfølging i 52 uker*

*Oxford kriteriene*

| | GET | CBT | Pacing | Spesialist |
|---|---|---|---|---|
| Antall | 159 | 155 | 159 | 157 |
| Alder år | 39 | 39 | 39 | 37 |
| Kvinner % | 77 | 80 | 76 | 76 |
| Psykiatri % | 46 | 47 | 47 | 48 |
| Antidepressiva % | 46 | 35 | 40 | 41 |

White PD et al Lancet 2011;377:823-36

# PACE studien

Resultater

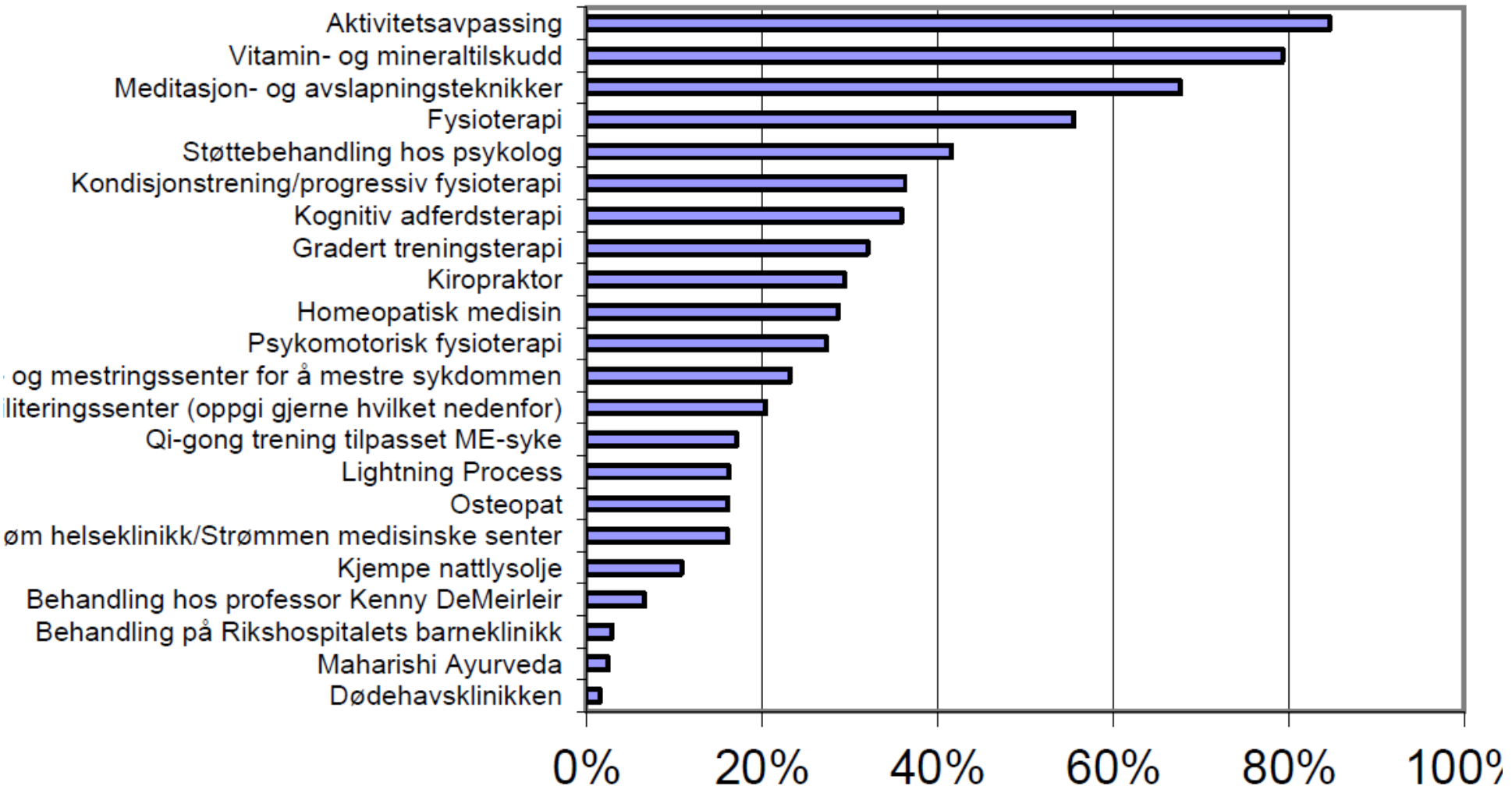
| | GET | CBT | Pacing | Spesialist |
|---|---|---|---|---|
| Fatigue skår 52 uker | 20,6 | 20,3 | 23.1 | 23.8 |
| **Fatigue skåre bedring** | **7,6** | **7,4** | **5.4** | **4.5** |
| | | | | |
| 6 min gange meter start | 312 | 333 | 314 | 326 |
| 6 min gange meter 1 år | 379 | 354 | 334 | 348 |
| **Økning meter** | **67** | **21** | **20** | **22** |

**Fatigue skår i engelske befolkning < 18**
**6 min gangtest ODS 660 meter**

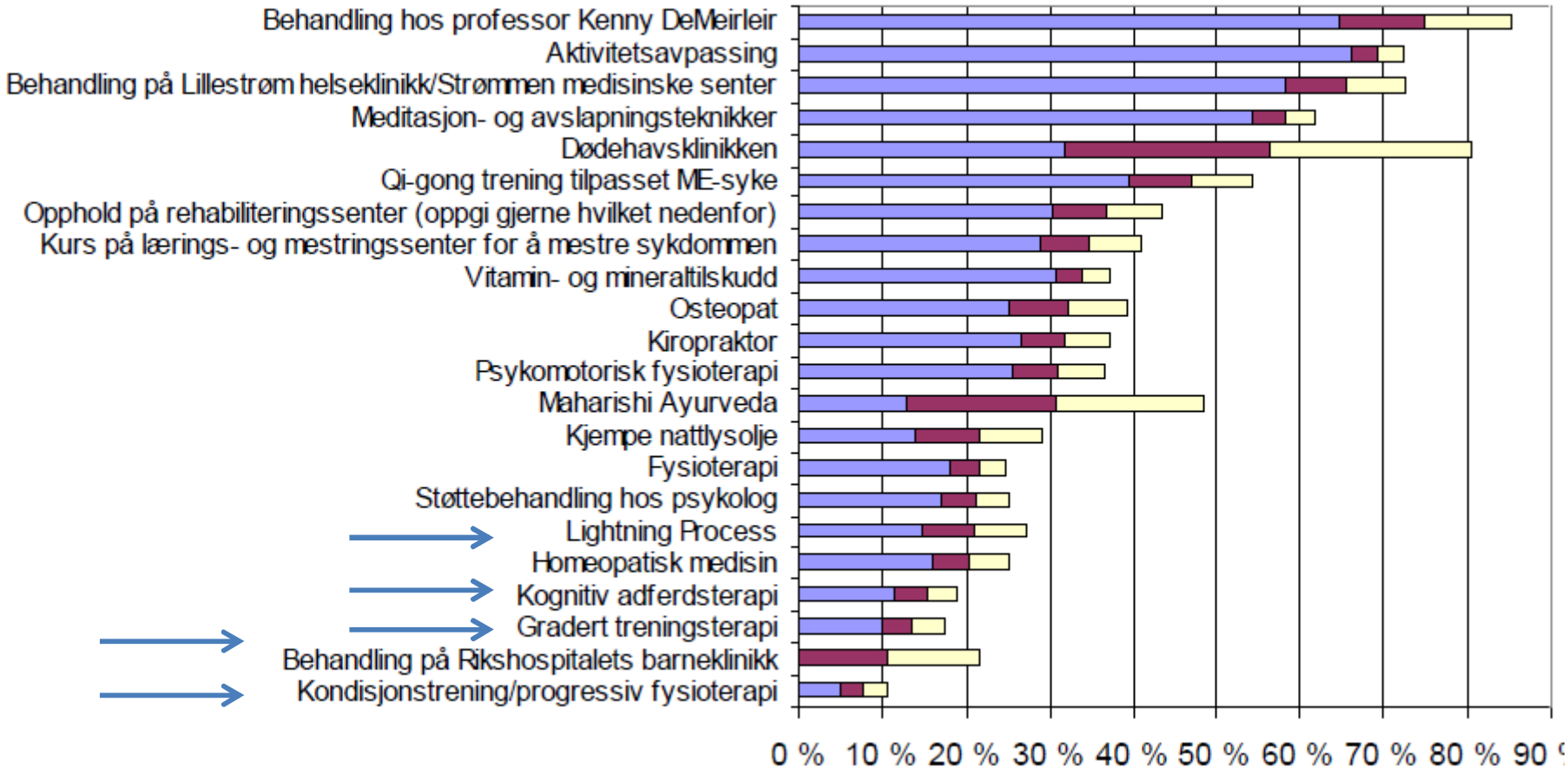
# Can patients with chronic fatigue syndrome really recover after graded exercise or cognitive behavioural therapy? A critical commentary and preliminary re-analysis of the PACE trial

**To cite this article:** Carolyn Wilshire, Tom Kindlon, Alem Matthees & Simon McGrath (2017) Can patients with chronic fatigue syndrome really recover after graded exercise or cognitive behavioural therapy? A critical commentary and preliminary re-analysis of the PACE trial, Fatigue: Biomedicine, Health & Behavior, 5:1, 43-56, DOI: 10.1080/21641846.2017.1259724

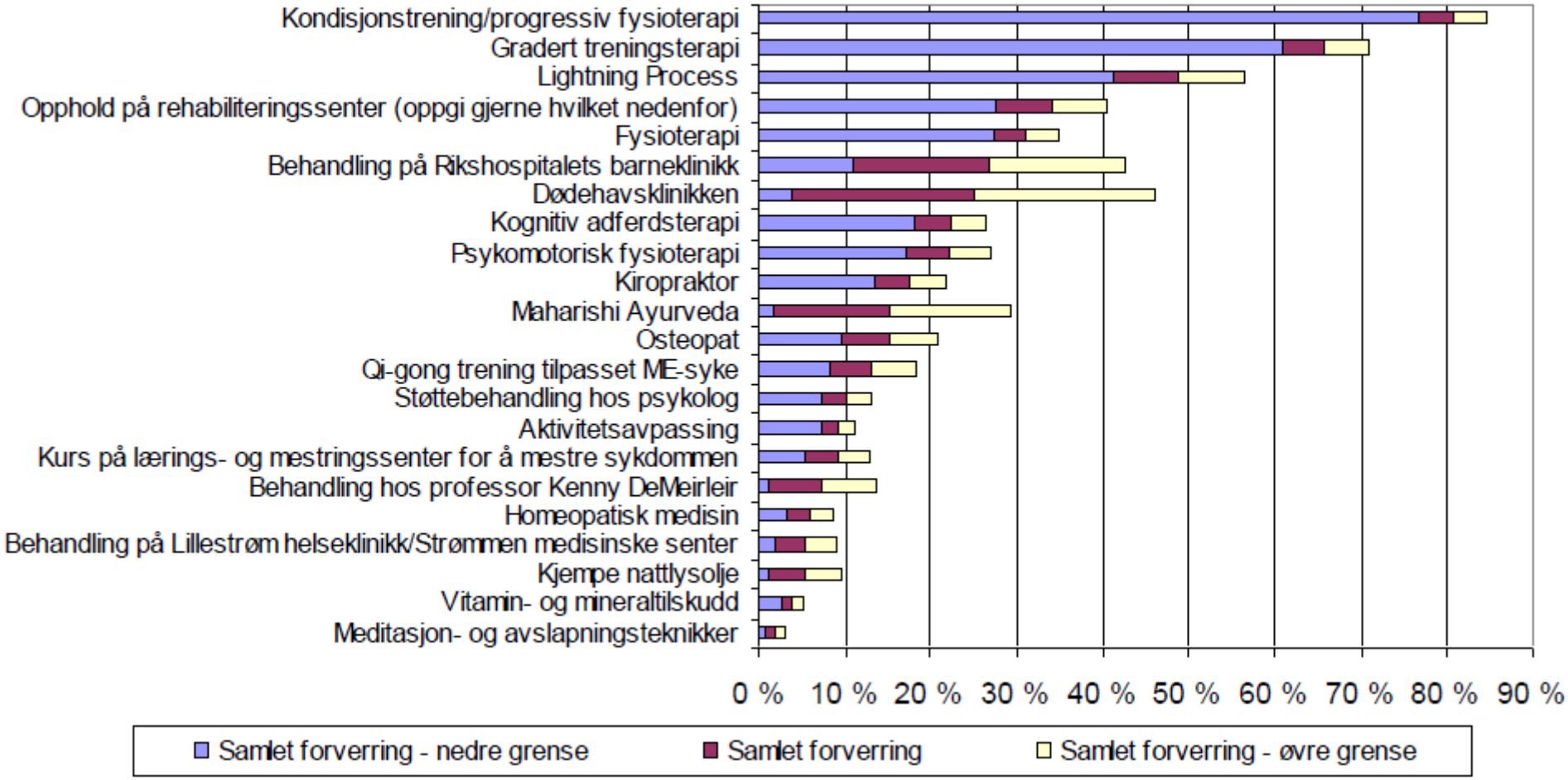
# Graf 10. Andel som har prøvd de ulike tilbudene



## Graf 12. Samlet forbedring (forbedring + stor forbedring)



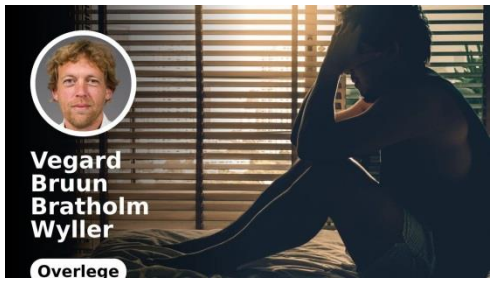
## Graf 13. Samlet forverring (forverring + stor forverring)



# Effekten av behandling ved ME

| Behandling | Til god hjelp | Ingen effekt | Forverring |
|---|---|---|---|
| Smertestillende | 61% | 28% | 11% |
| Sovemedisin | 67% | 17% | 16% |
| Pacing Aktivitetsavpasning ca 70% | 89% | 9% | 2% |
| Gradert trening Ignorerer symptomer øker litt hver dag | 34% | 16% | 50% |
| Kostendring | 65% | 32% | 3% |
| Hvile | 91% | 8% | 1% |
| Kognitiv adferdsterapi | 7% | 67% | 26% |
| | | | |

Brukerundersøkelse i UK 2001




**Feilinformasjon om ME kan skremme pasienter fra dokumentert behandling | Vegard Bruun Bratholm Wyller**
Mitt råd til ME-pasienter: Ikke lytt til Ola Didrik Saugstads udokumenterbare svartmaling.
**Vegard Bruun Bratholm Wyller, professor og overlege, Akershus universitetssykehus**
**DEBATT** 10. okt. 2017

Saugstads feilinformasjon om ME kan skremme pasienter fra å forsøke dokumentert behandling. Jeg gjentar derfor mitt innstendige råd: Ikke lytt til Saugstads udokumenterte svartmaling, men forsøk kognitiv terapi eller beslektede behandlingsformer! Forskning viser at risikoen er minimal, mens den mulige gevinsten er stor. I beste fall kan man bli frisk.


**Det er ikke riktig at risikoen ved LP og kognitiv adferdsterapi er minimal | Ola Didrik Saugstad**
Her går det viktigste skillet i ME-debatten.
**DEBATT** 22. okt. 2017
**Ola Didrik Saugstad** Professor I i barnesykdommer, Universitetet i Oslo

Brukerundersøkelser viser at 10ï 50 prosent blir dårligere av behandling som kognitiv adferdsterapi (KAT) og Ligthening Process (LP), skriver innleggsforfatteren.

# Er det en neuroinflammasjon ved ME?

# Neuroinflammasjon ved ME/CSF

Mange karakteristikker ved ME antyder at immunsystemet er aktivert i hjernen, noe som fører til frigjøring av betennelsesstoffer

Denne nevroinflammasjonen vil føre til en rekke symptomer som fatigue, smerte, kognitive problemer og søvnforstyrrelser

En hypotese er at aktiverte immunceller fra andre steder i kroppen inflitrerer hjernen, noe som fører til ME symptomer

Et nytt forskningsprosjekt ved Univ Alabama prøver å følge perifere immunceller og undersøke om de krysser blod-hjernebarrieren

*Yonger J ME Research UK Januar 2019*

# Brain Science on ME/CSF

PET studier har vist at neuroinflammasjon finnes utbredt in hjernene til ME/CSF pasienter  og er assosiert med alvorligheten av symptomene

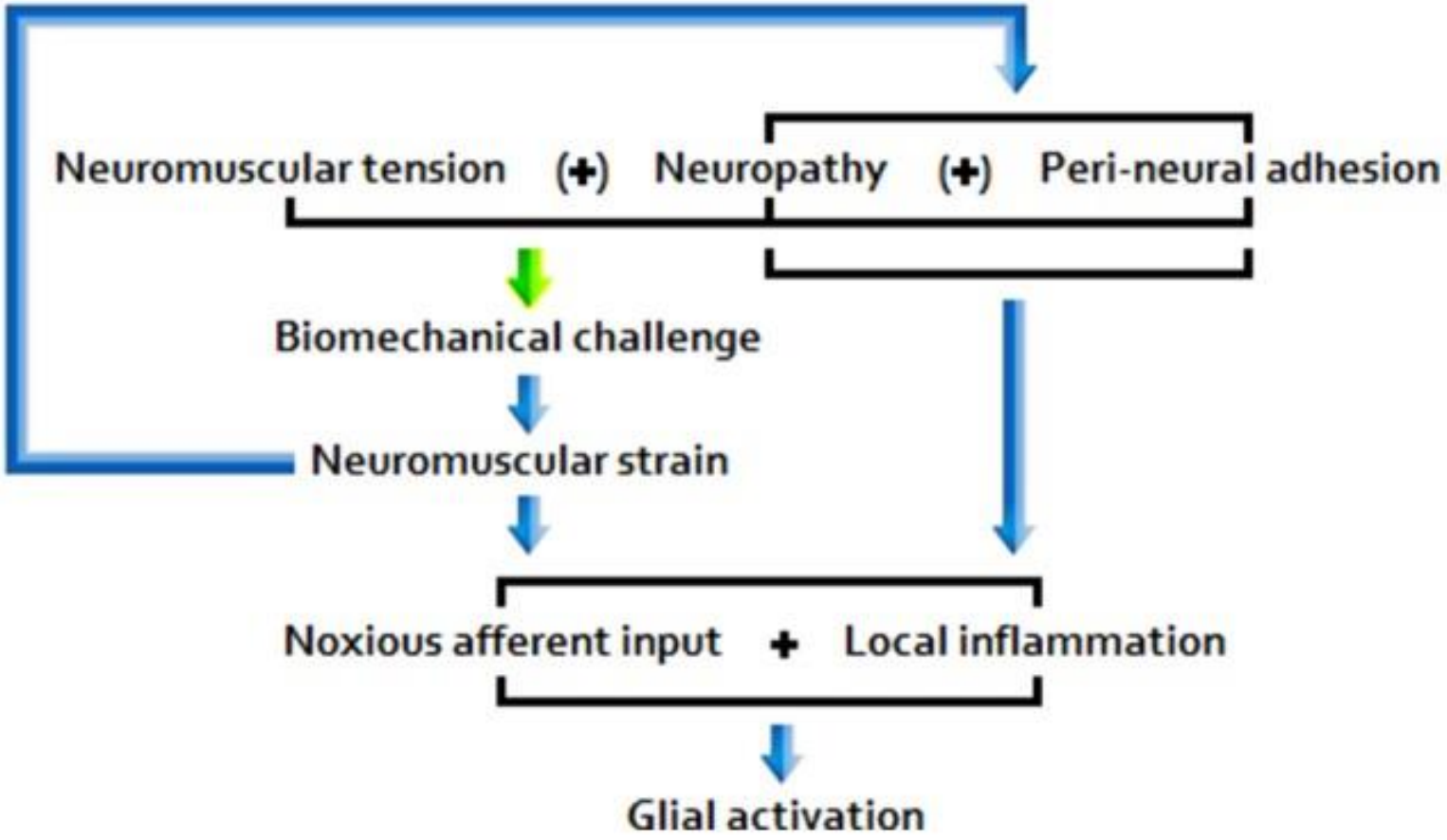
*Watanbe Y  Brain and Nerve 2018;70:*

Vi argumenter for at hoveddelen av ME/CSF neuroimaging ikke har brukt en optimal teknikk for å studere hjernestammen, til tross for dens sansynlige sentrale rolle ved enhver neuroinflammatorisk tilstand og dets effekter på det autonome nervesystemet. Heller ikke cytokinprofilen er konsistent

*Van Elzakker MB et al Frontiers in Neurology 2019;9:1-29*

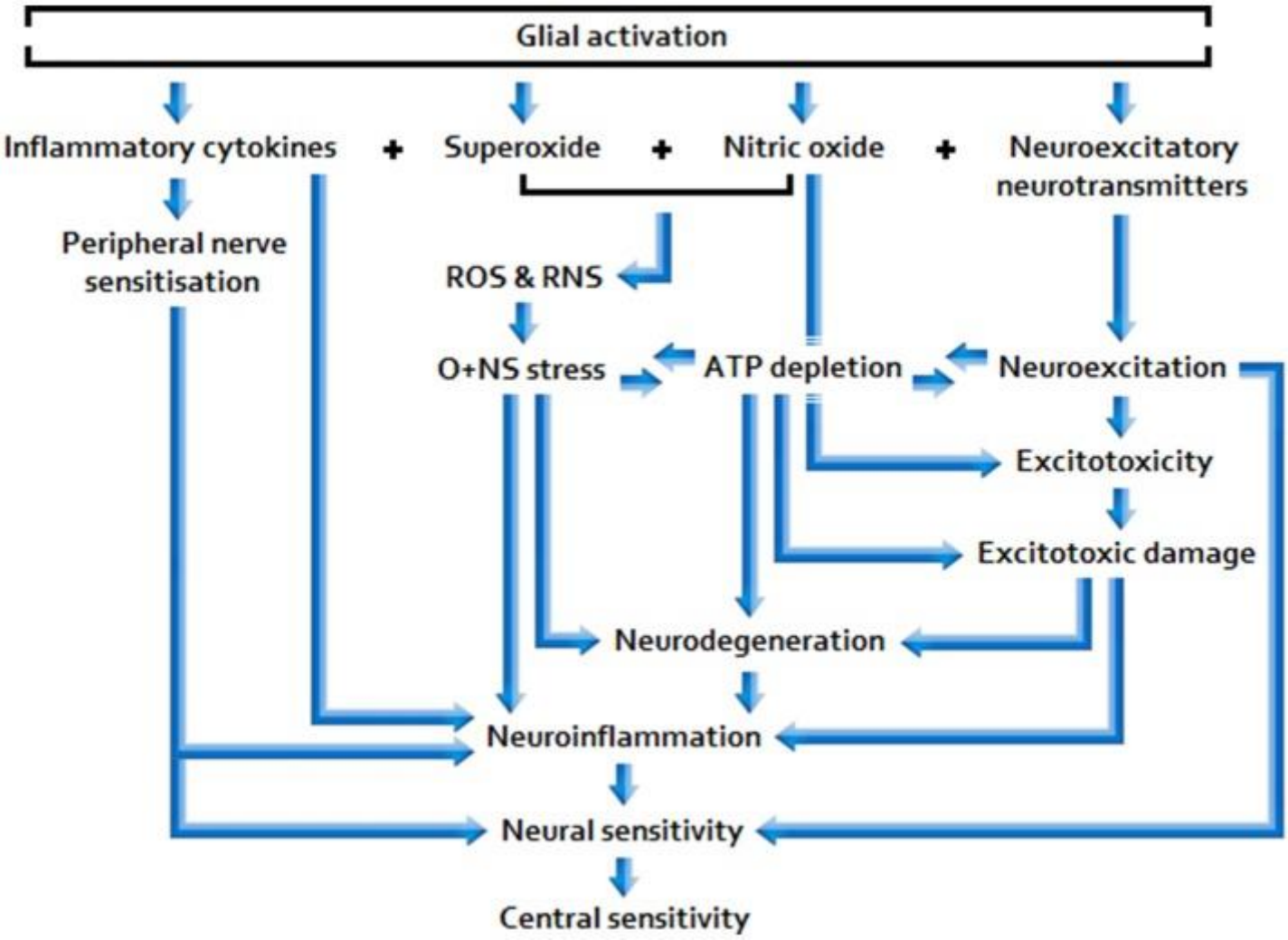
Chronic peripheral nociception/neuroinflammation associated with encumbrance of neuromuscular/osseous tissues

**Encumbrance pathway ñAò**



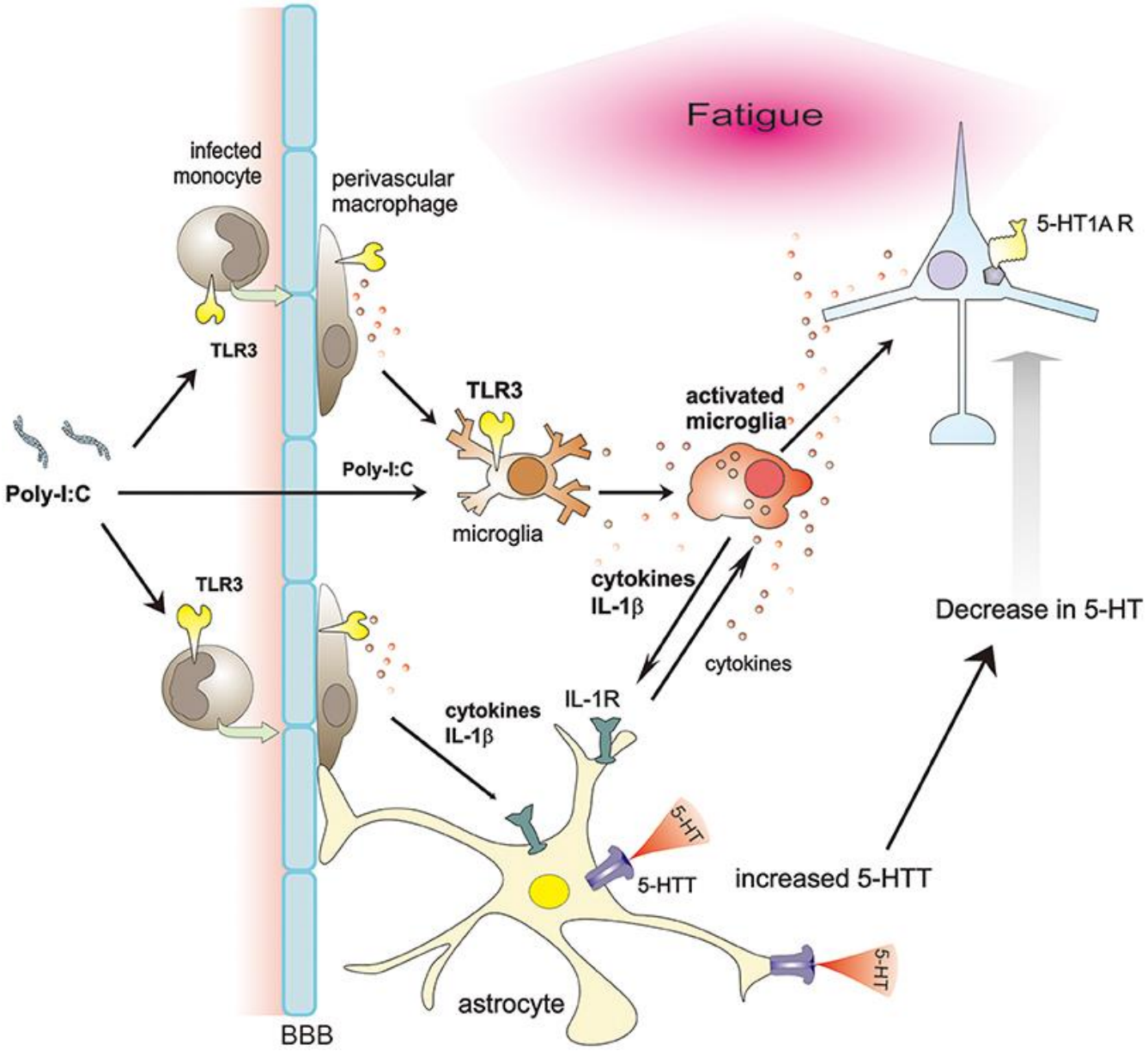

**The Neuroinflammatory Etiopathology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome(ME/CFS).** Glassford JA[1]. Front Physiol. 2017 Feb 17;8:88

**Effects of sustained glial activation**.




The picture that emerges from the literature indicates that disease pathogenesis is a function of the following primary etiopathologies

# Hypotese for aktivering av glia celler og fatigue ved CFS




*Noda M et al Frontiers in Psychiatry 2018;9:589-*

Poly C øker permeabilitetetn til blod-hjernebarrieren og aktiverer mikroglia. Disse skiller ut cytokiner. Il-1beta oppregulerer serotinin transportør noe som fører til lavere serotonin utenfor cellene, noe som kan indusere fatigue

# ME ï  hvor lenge skal vi vente?

**Kjenner vi årsaken?**
**Finner vi biomarkører?**
**Blir det noen behandling?**

Vi er på vei dit é
Men det kan fortsatt ta litt tid