



University of  
BRISTOL



# Chronic Fatigue Syndrome

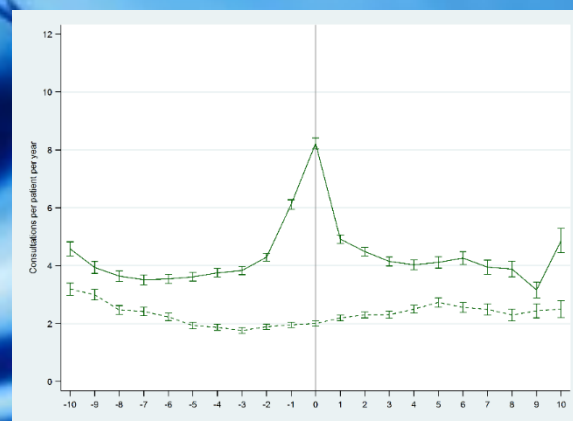
Everything you need to know

Esther Crawley

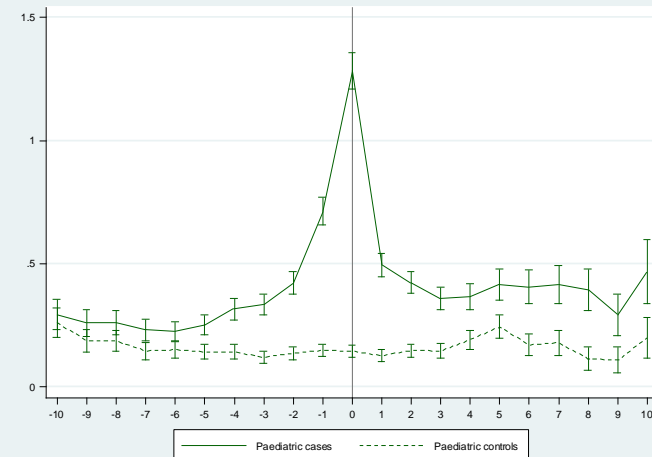
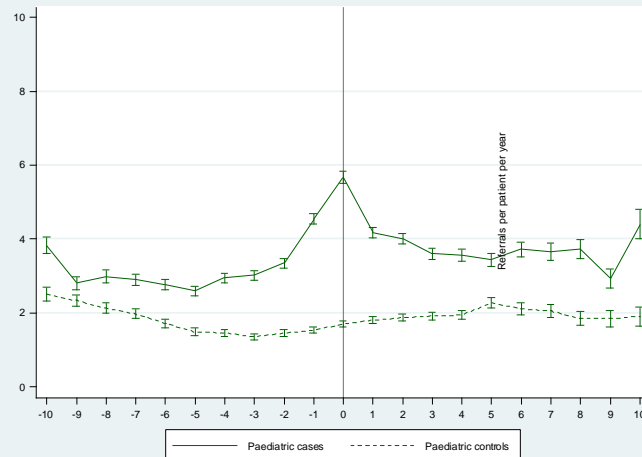
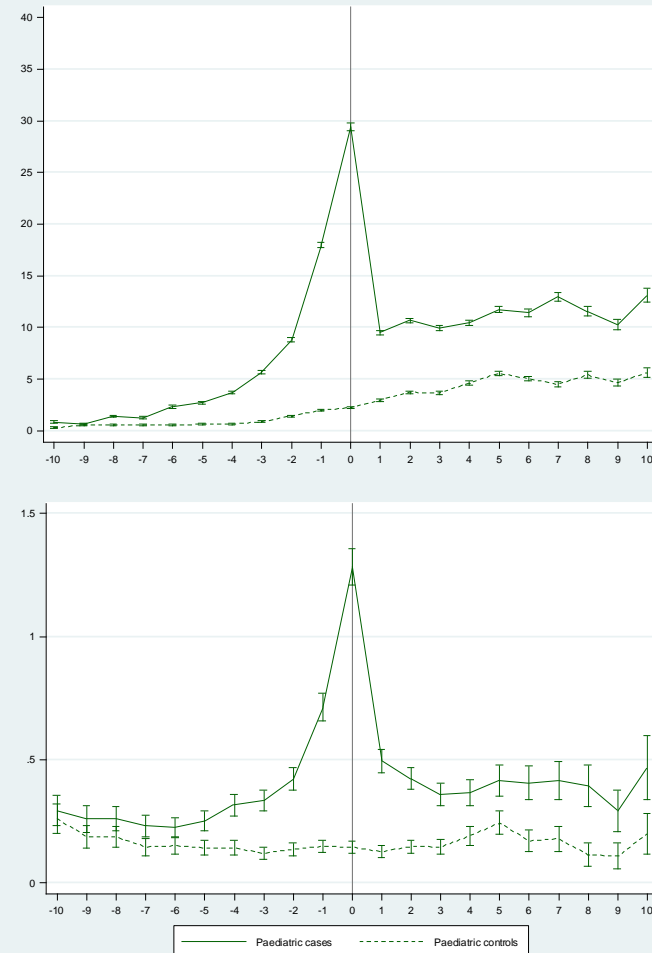
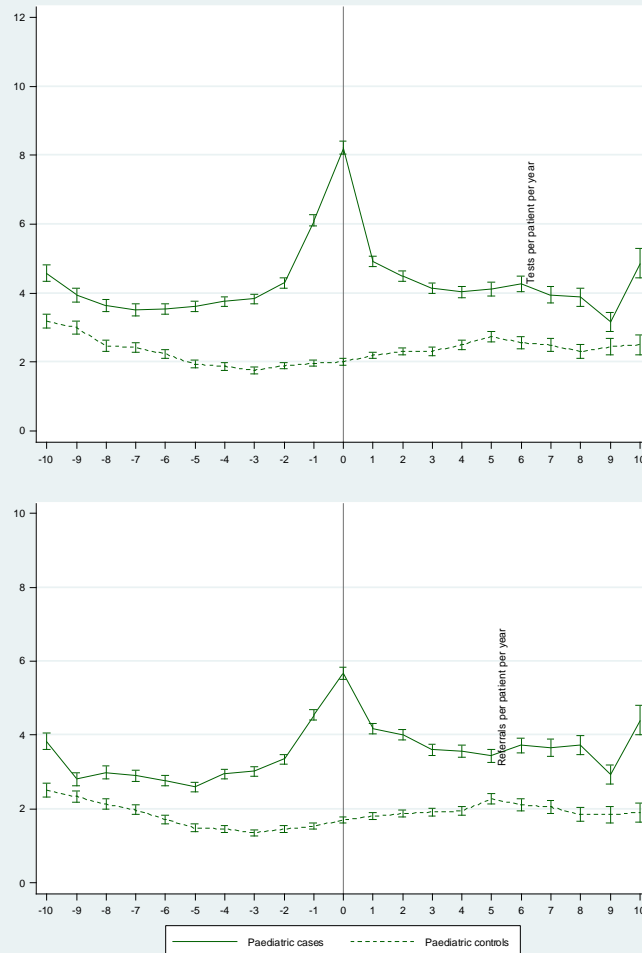








# Rates of GP consultations, tests, prescriptions and referrals from 10 years before until 10 years after a first recorded diagnosis of CFS/ME in paediatric cases compared with controls





# In this talk

- A case
- Making a diagnosis
- What to tell children/families
- Treatment options
  - ❖ What you can do
  - ❖ Specialist treatment
- Questions
- Research updates

# Case: Iris

- 15 year old girl
- 2 years ago: episode of “gastric flu”
- Since then:
  - ❖ nausea
  - ❖ problems concentrating
  - ❖ fatigue
  - ❖ abdominal pain
  - ❖ headaches
  - ❖ dizzy

# Iris (2)

- Used to be an athlete (show jumping)
- Now attending school 30% time



# In the last year

- 2 gastroenterologists: Investigated for:
    - ❖ Peptic ulcer disease
    - ❖ Gastro-eosophageal reflux
    - ❖ Celiac disease
    - ❖ Bacterial overgrowth
    - ❖ Δ: Irritable Bowel Syndrome.
  - 1 nephrologist + 2 urologists
    - ❖ Multiple investigations. Diagnosis?
  - Gynaecologist
  - 1 ENT surgeon ?labyrinthitis
  - Neurologist Δ migraine
  - Psychiatrist Δ depressive disorder.
- Abdominal pain**
- Dizziness**
- Headaches**

# What happened

- Referred to social services “unwell no cause found”
- Child protection register:
  - ❖ Missing school
  - ❖ Multiple doctors
  - ❖ No cause for school absence
  - ❖ **Diagnosis ??**

# Extra history

- Sleep: “No matter how much I sleep I still feel just as tired when I wake up”
- (13 hours at night, 2 hours afternoon)
- Post-exertional malaise
- No mood disorder

# Make a diagnosis

# Chronic Fatigue Syndrome (CFS/ME)

- *“persistent or debilitating fatigue that is not lifelong, the result of ongoing exertion, alleviated by rest, explained by other conditions and that results in a substantial reduction in activity”*
- Children 3 months, adults 4 months
- Additional symptoms (1-4 depending on definition)

*Fukuda 1994, Reeves 2004, NICE 2007*

# Making a diagnosis

- Symptom, sleep and activity pattern
- Exclude other diagnoses:
  - ❖ Screening investigations;
    - FBC, ESR/viscosity, CRP, Us and Es, creatinine, LFTs, Creatinine kinase, Coeliac screen, Thyroid function, ferritin, Urine dip.
  - ❖ Other investigations:
    - BP, MRI etc.

# What symptoms?



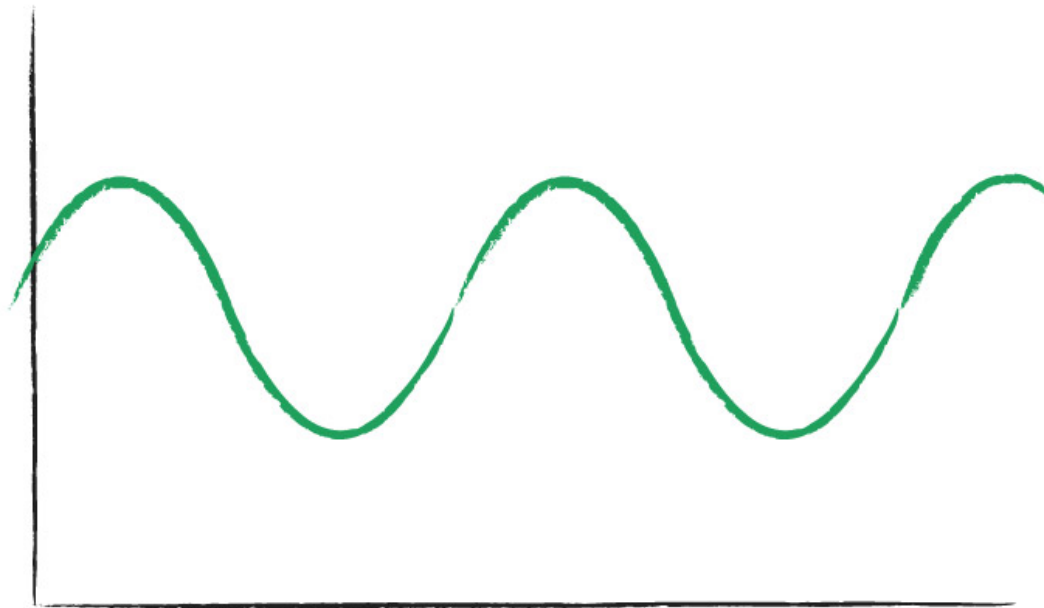
## Symptoms persisted/recurred during 3 (children) /6 (adult) or more consecutive months and did not predate the fatigue:

Symptom	Paediatric (N=866)	Adult (N=861)
Post-exertional malaise	97.5%	96.6%
Cognitive dysfunction	80.6%	96.3%
Sleep disturbance	94.8%	95.2%
Muscle pain	74.8%	87.9%
Joint pain	61.6%	73.3%
General malaise	72.9%	72.3%
Headaches	79.8%	67.8%
Sore throat	61.2%	47.9%
Dizziness	65.7%	46.0%
Painful lymph nodes	44.9%	38.0%
Nausea	61.1%	36.2%
Palpitations	31.3%	26.7%

# Problems with sleep

- Difficulty getting off to sleep
- Difficulty waking up
- Poor quality sleep
  
- Day night reversal
- Excessive sleeping

# Typical pattern of activity



# What I tell children

## The Epidemiology

# How common is it in secondary schools?

- 1% of secondary school children miss a day a week because of CFS/ME
- Only 1:10 have been given a diagnosis
- About 2% have CFS/ME at 13, 15 and 18
- Probably 1:1000 children are so severely affected they do not attend school at all



# Prevalence at different ages, according to gender.









## Original article

# Phenotypes of chronic fatigue syndrome in children and young people

Margaret May<sup>1</sup>, Alan Emond<sup>2</sup>, Esther Crawley<sup>2</sup>

<sup>1</sup>Department of Social Medicine, Bristol University, Bristol, UK

<sup>2</sup>Centre for Child and Adolescent Health, Bristol University, Bristol, UK

## ABSTRACT

**Objective** To investigate the heterogeneity of chronic fatigue syndrome (CFS/ME) in children and young people.

**Setting** Regional specialist CFS/ME service

**Patients** Children and young people aged <19 years

## What is already known

► CFS/ME is a complex condition affecting children and young people



► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2016-311293>)

<sup>1</sup>School of Social & Community Medicine, University of Bristol, Bristol, UK

**Obesity in children and young people: a population birth cohort study**  
Tom Norris, <sup>1</sup> Kevin Deere, <sup>1</sup> Jon H. Tobias, <sup>1</sup> and Esther Crawley<sup>2</sup>  
<sup>1</sup>Centre for Child and Adolescent Health, School of Clinical Sciences, Bristol, United Kingdom; <sup>2</sup>Musculoskeletal Research Unit, School of Clinical Sciences, Bristol, United Kingdom

**ABSTRACT** Identify the prevalence of obesity in children and young people (CYP) with chronic fatigue syndrome (CFS) compared with healthy adolescents, and those identified with CFS in a population cohort.  
**Design** Cross-sectional analysis of multiple imputed data.

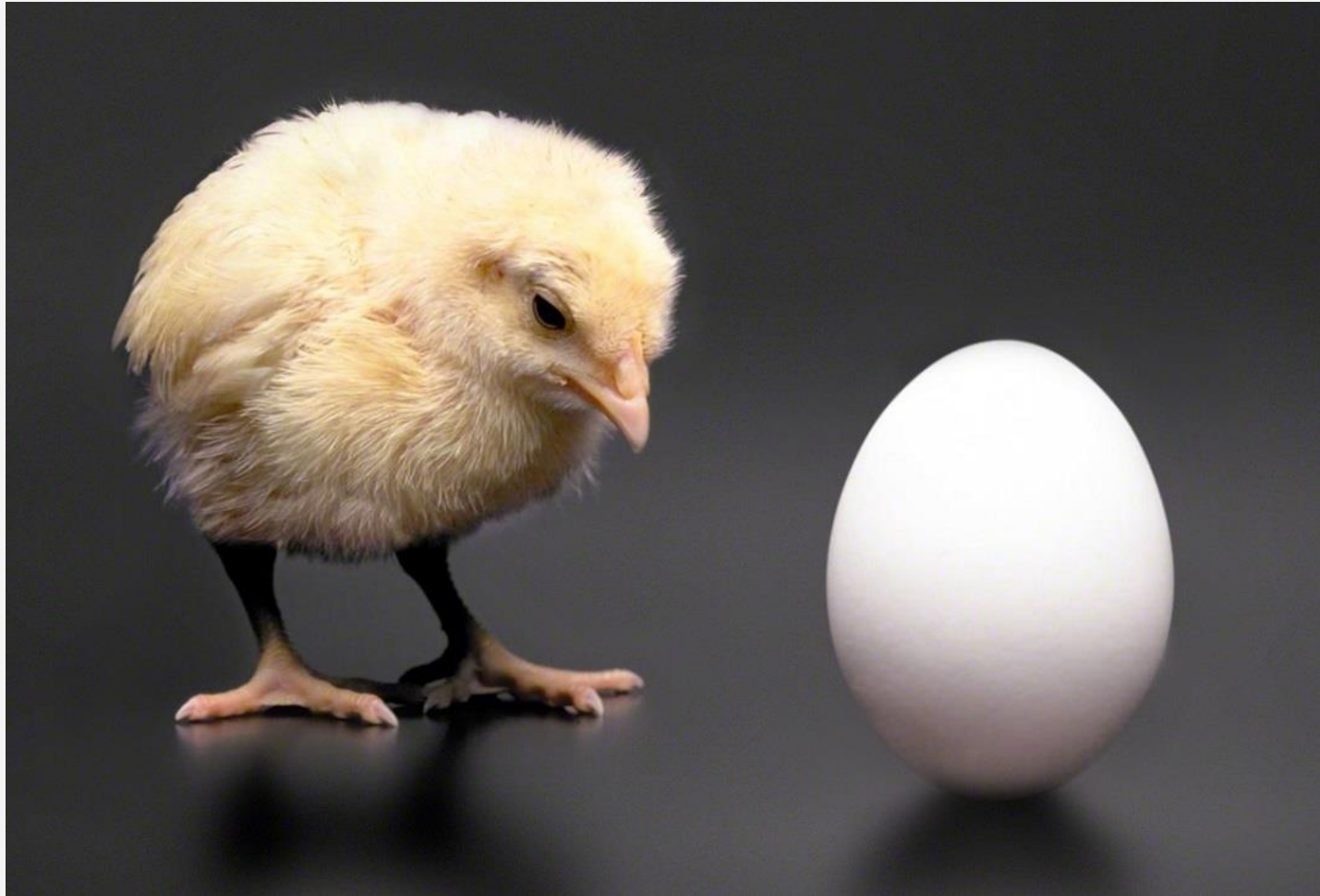
Original article  
The Journal of Pain, Vol 17, No 1 (Feb), 2016; pp 1-10  
Available online at [www.jpain.org](http://www.jpain.org) and [www.sciencedirect.com](http://www.sciencedirect.com)



29%



38%



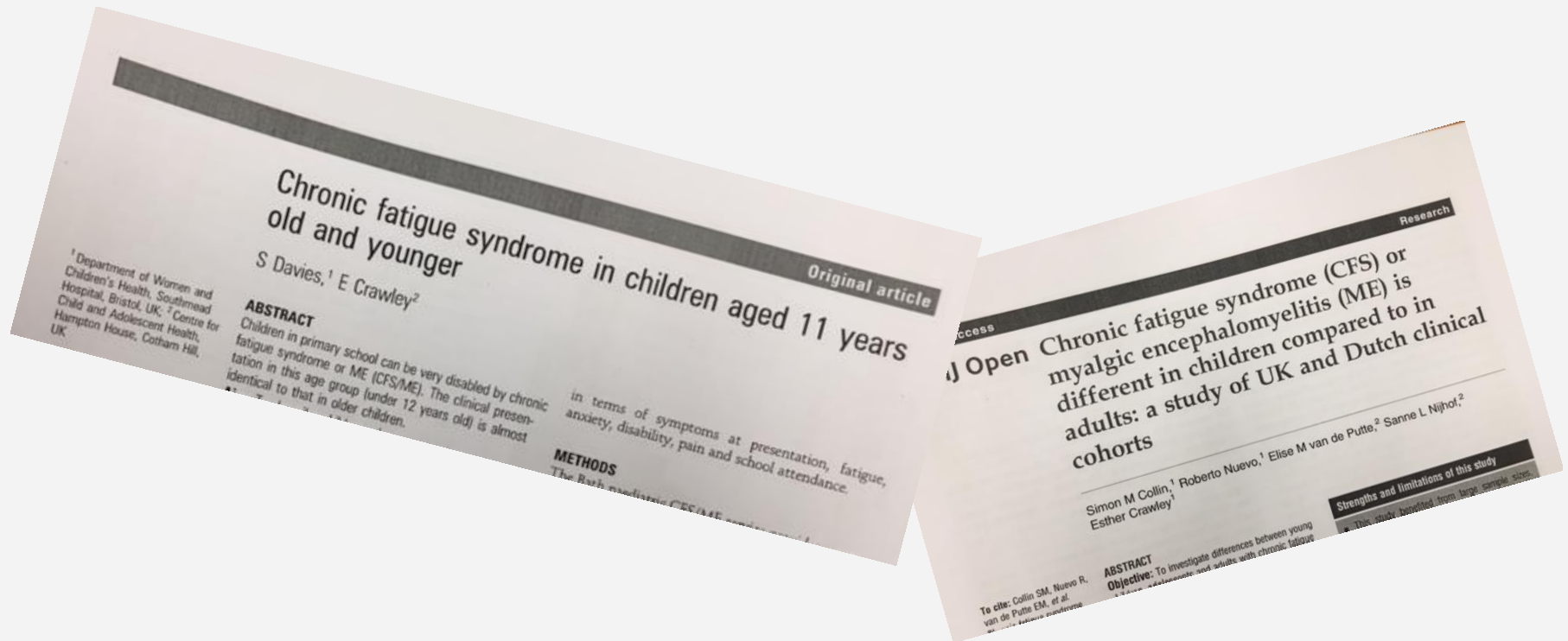
**“Your stuck at home, so everything you’d enjoy, going out, then coming home and being able to sit with your family but obviously if you’re sat at home all day then all night, and then all day the next day you just get bored of the same four walls.”**

**“I wanted a career in basketball. But now it’s not looking too good....”**

**“I remember at prom, I remember everyone else dancing and I was the only one sat down. And ohh...like....like... it was horrible.”**

**“I am worried that I am going to return, and they are going to be so far ahead of me....”**

# What about primary school children?



# Primary school children

- Less likely:
  - ❖ Cognitive problems
  - ❖ Headaches
  - ❖ Problems with sleep
- More likely:
  - ❖ Sore throats & tender lymph nodes
  - ❖ Dizziness

Collin SM 2015

# What causes CFS/ME?



# Risk Factors - adults

- Risk factors:
  - ❖ Female
  - ❖ Genes
  - ❖ Socio-economic deprivation
  - ❖ Ethnic minorities
  - ❖ Older age
  - ❖ Infections/Infection severity
  - ❖ Mood

Hempel '08 Bhui '11 Hickie '06,

# Risk Factors – children?

- Risk factors:
  - ❖ Female ✓
  - ❖ Genes ✓
  - ❖ Socio-economic deprivation ✓
  - ❖ Infections/Infection severity ✓
  - ❖ Ethnic minorities ?
  - ❖ Older age ?
  - ❖ Mood ?

Hempel '08 Katz '11 '12 Hickie '06, Crawley 09

# Prevalence at different ages, according to gender.



# Genes

- Twin studies: moderate genetic risk

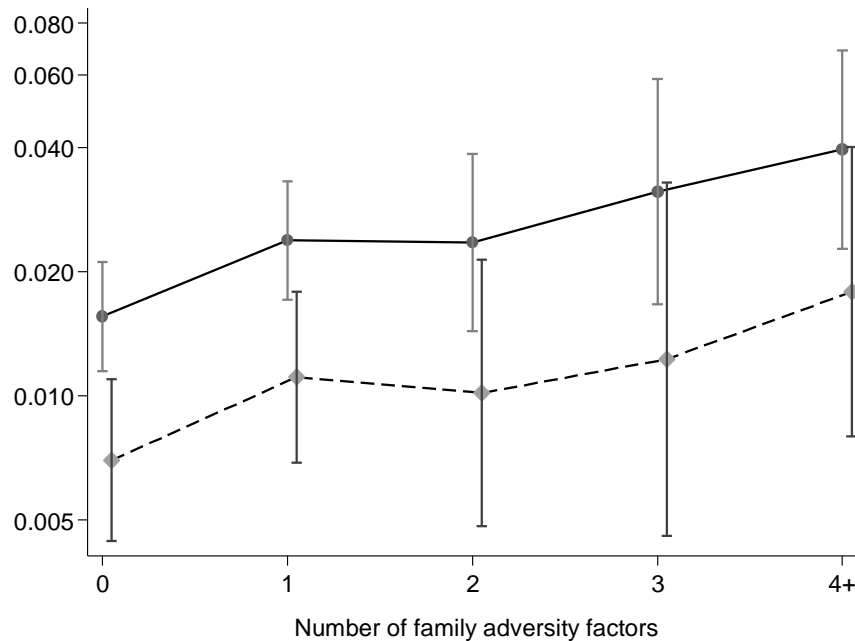


# Genes

- CFS/ME clusters within families
- Early age of onset ↑ heritability

# Odds of developing CFS/ME for summated Family Adversity Index (N = 5657)

The risk of CFS/ME increases with family adversity score (OR 1.25, 95% CI 1.09, 1.43.)



*Housing*  
*Education*  
*Financial pressures*  
*Relationship*  
*Substance abuse*  
*Crime*

Continuous = 3 months    Dashed = 6 months

# Infection

Cite this article as: BMJ, doi:10.1136/bmj.38933.585764.AE (published 1 September 2006)

Research

BMJ

## Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study

Ian Hickie, Tracey Davenport, Denis Wakefield, Ute Vollmer-Conna, Barbara Cameron, Suzanne D Vernon, William C Reeves, Andrew Lloyd, for the Dubbo Infection Outcomes Study Group

### Abstract

**Objective** To delineate the risk factors, symptom patterns, and longitudinal course of prolonged illnesses after a variety of acute infections.

have been linked to a diverse spectrum of infections, including brucellosis (which is caused by an intracellular bacterium),<sup>7</sup> glandular fever (caused by the herpesvirus Epstein-Barr virus),<sup>8</sup> Lyme disease (caused by infection with the tickborne spirochaete *Borrelia burgdorferi*).<sup>9</sup> O fever (caused by the intracellular



# Vaccines

- Flu vaccine
- HPV vaccine



Contents lists available at ScienceDirect

## Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)



# Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine



Per Magnus<sup>a,\*</sup>, Nina Gunnes<sup>a</sup>, Kari Tveito<sup>b</sup>, Inger Johanne Bakken<sup>a</sup>, Sara Ghaderi<sup>a</sup>, Camilla Stoltenberg<sup>a</sup>, Mady Hornig<sup>c</sup>, W. Ian Lipkin<sup>c</sup>, Lill Trogstad<sup>a</sup>, Siri E. Håberg<sup>a</sup>

<sup>a</sup> Norwegian Institute of Public Health, 4404 Nydalen, 0403 Oslo, Norway

<sup>b</sup> Journal of the Norwegian Medical Association, Oslo, Norway

<sup>c</sup> Center for Infection and Immunity, Columbia University, NY, NY, USA

### ARTICLE INFO

#### Article history:

Received 10 June 2015

Received in revised form

22 September 2015

Accepted 6 October 2015

Available online 17 October 2015

### ABSTRACT

**Background:** Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated to infections and it has been suggested that vaccination can trigger the disease. However, little is known about the specific association between clinically manifest influenza/influenza vaccine and CFS/ME. As part of a registry surveillance of adverse effects after mass vaccination in Norway during the 2009 influenza A (H1N1) pandemic, we had the opportunity to estimate and contrast the risk of CFS/ME after infection and vaccination.



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

## Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)



### No evidence found for an increased risk of long-term fatigue following human papillomavirus vaccination of adolescent girls



T.M. Schurink-van't Klooster<sup>a,\*</sup>, J.M. Kemmeren<sup>a</sup>, N.A.T. van der Maas<sup>a</sup>, E.M. van de Putte<sup>b</sup>,  
M. ter Wolbeek<sup>c</sup>, S.L. Nijhof<sup>b</sup>, A.M. Vanrolleghem<sup>d</sup>, J.A. van Vliet<sup>a</sup>, M. Sturkenboom<sup>e</sup>, H.E. de Melker<sup>a</sup>

<sup>a</sup> Center for Infectious Diseases Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

<sup>b</sup> Department of Paediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

<sup>c</sup> Department of Woman & Baby, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

<sup>d</sup> Department of Medical Informatics, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands

<sup>e</sup> Julius Global Health, University Medical Center Utrecht, the Netherlands

# Mood problems

# Mood as risk factor

## ❖ Adults:

- Psychiatric diagnosis risk factor (OR 2.65 CI 1.26-5.57,  $p=0.01$ )

## ❖ Young people:

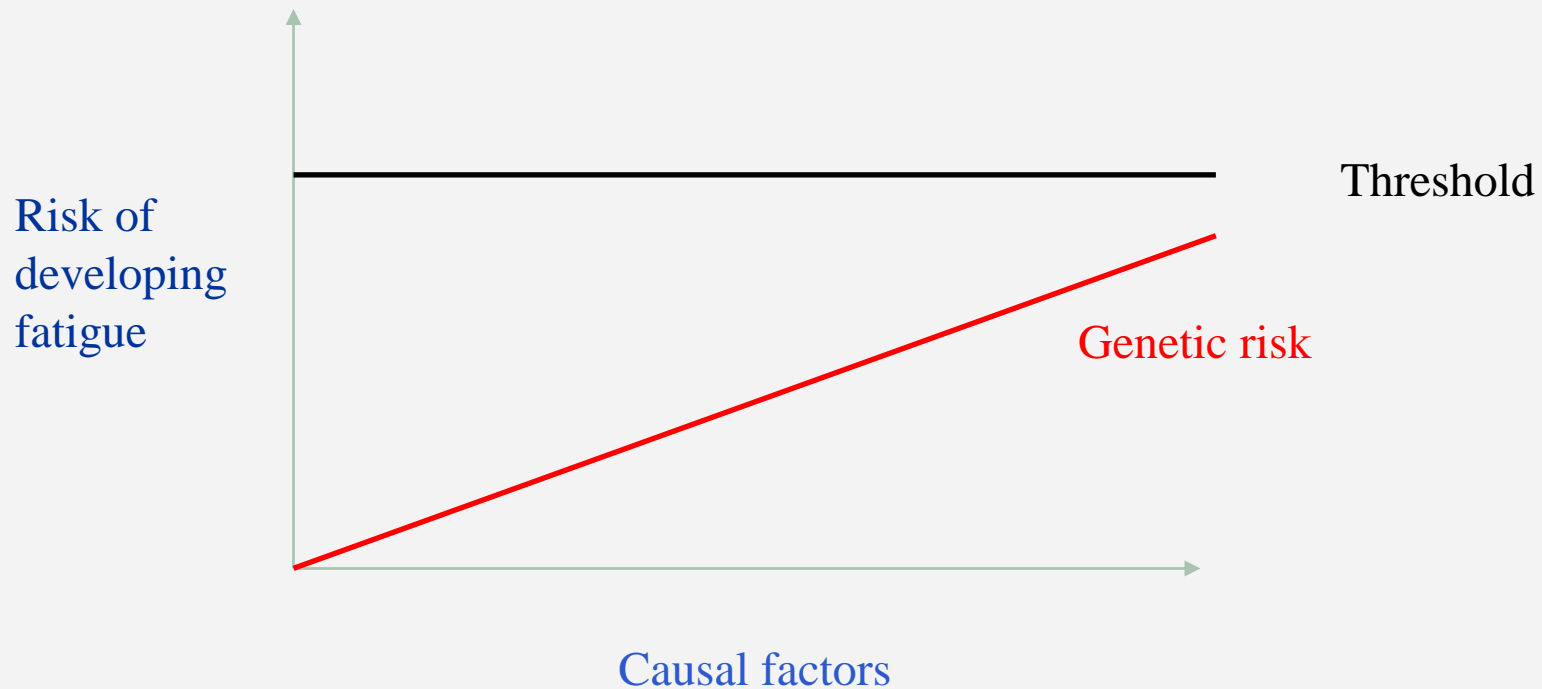
- CFS/ME in adults not predicted psychological distress in children
- Anxiety & depression not predictive CFS
- Some evidence mood predicts fatigue

*Harvey 2008; Clark '11 ter Wolbeek '11 Viner 2004; Rimes 2007*

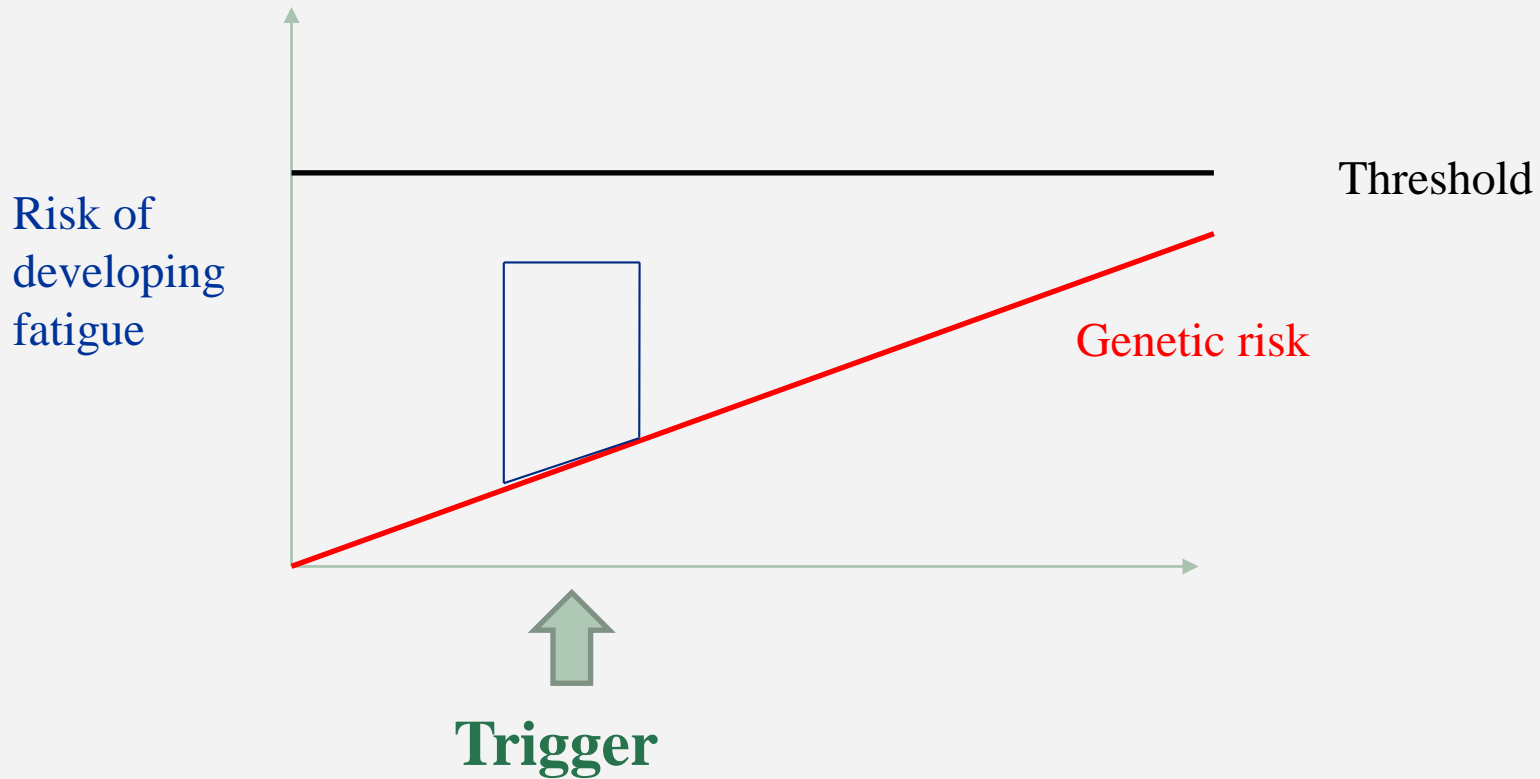
# Mood prior to assessment

Symptom	Paediatric (N=218)	Adult (N=861)
Co-morbid depression	9.6%	34.6%
Co-morbid anxiety	14.4%	34.1%
Irritable Bowel Syndrome	6.5%	30.7%
Fibromyalgia/Chronic Widespread Pain	1.8%	29.0%
Migraine	13.3%	21.6%
Chronic Regional Pain Disorder	2.3%	2.8%

# A model to consider

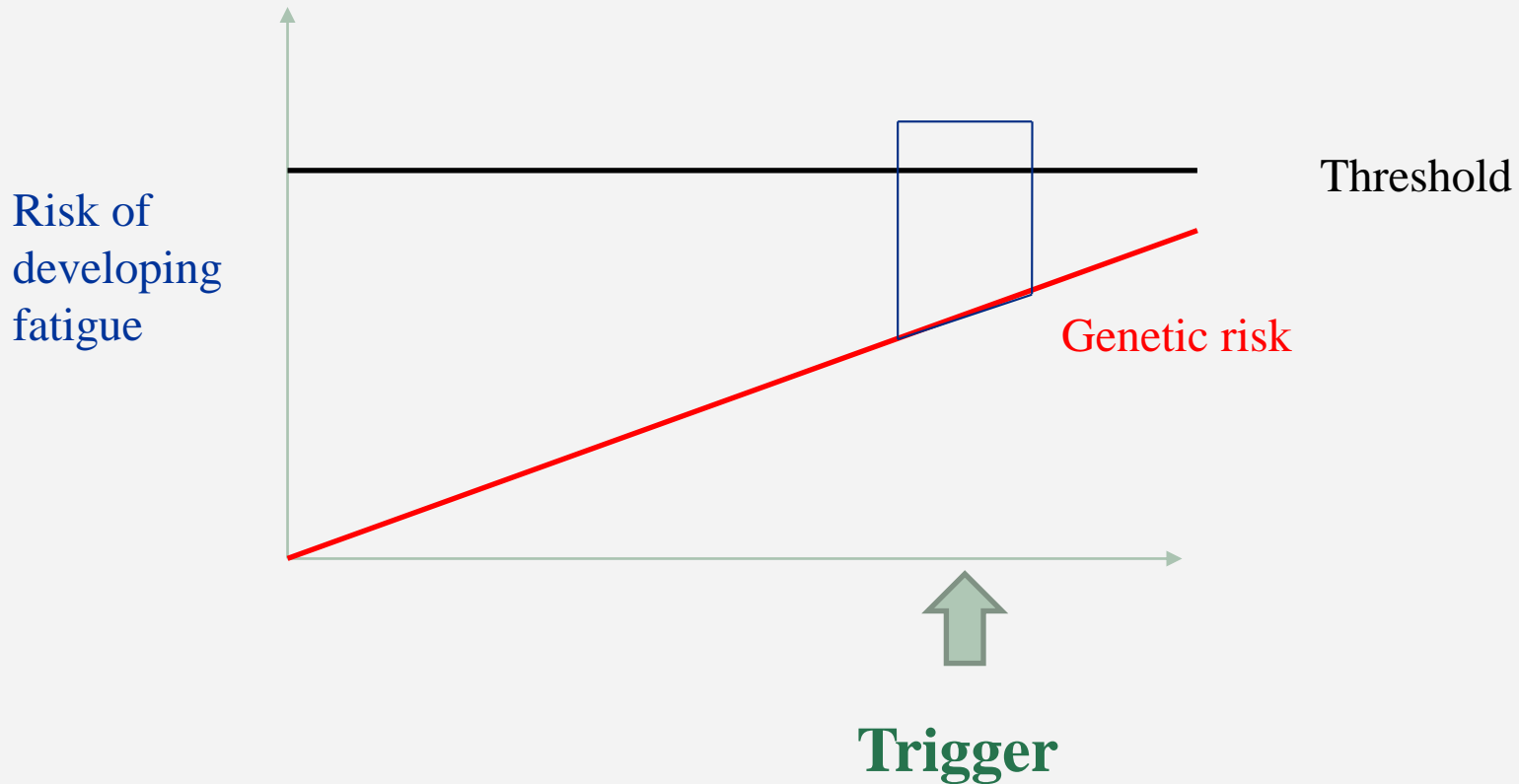


# A model to consider

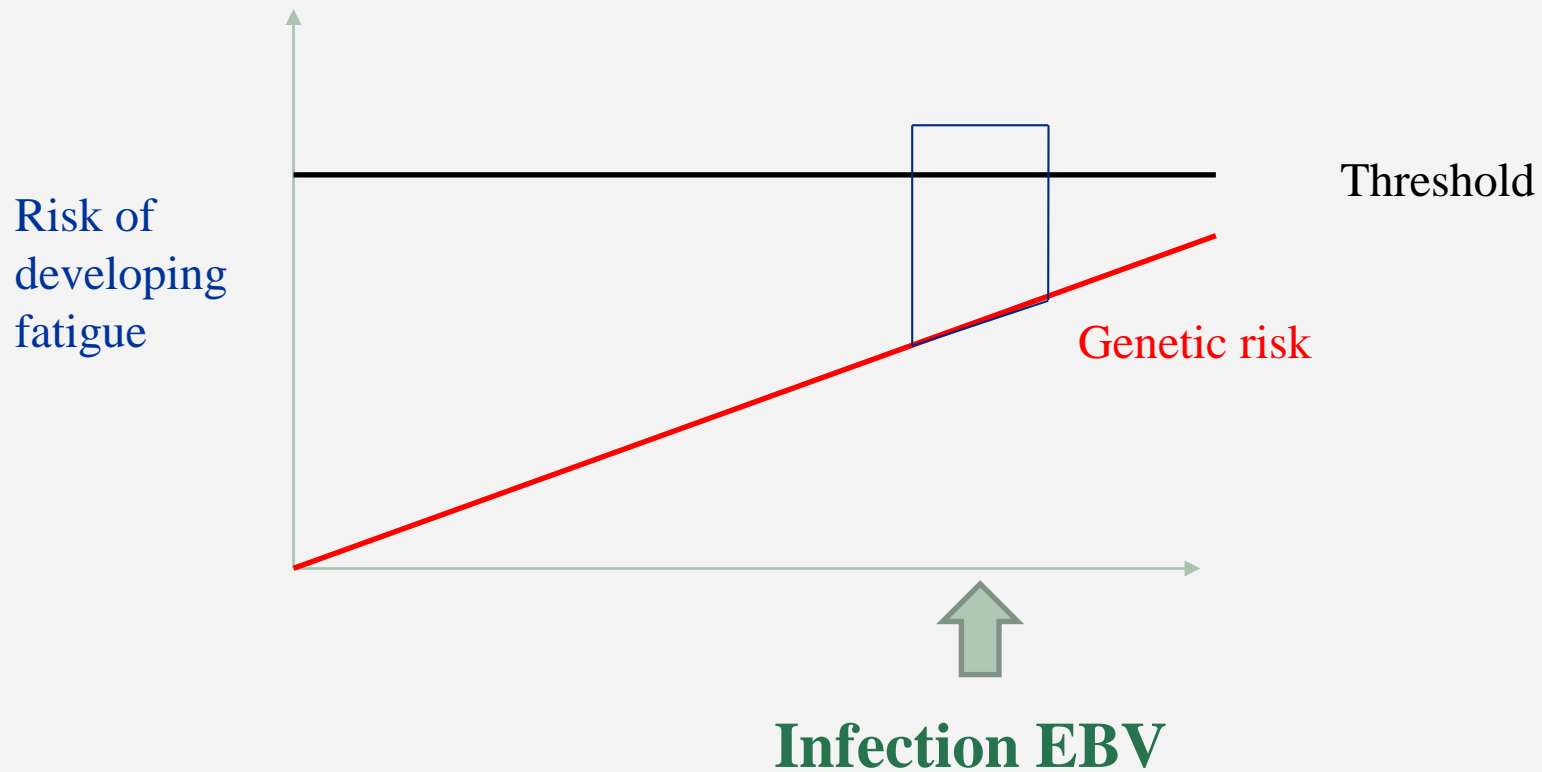




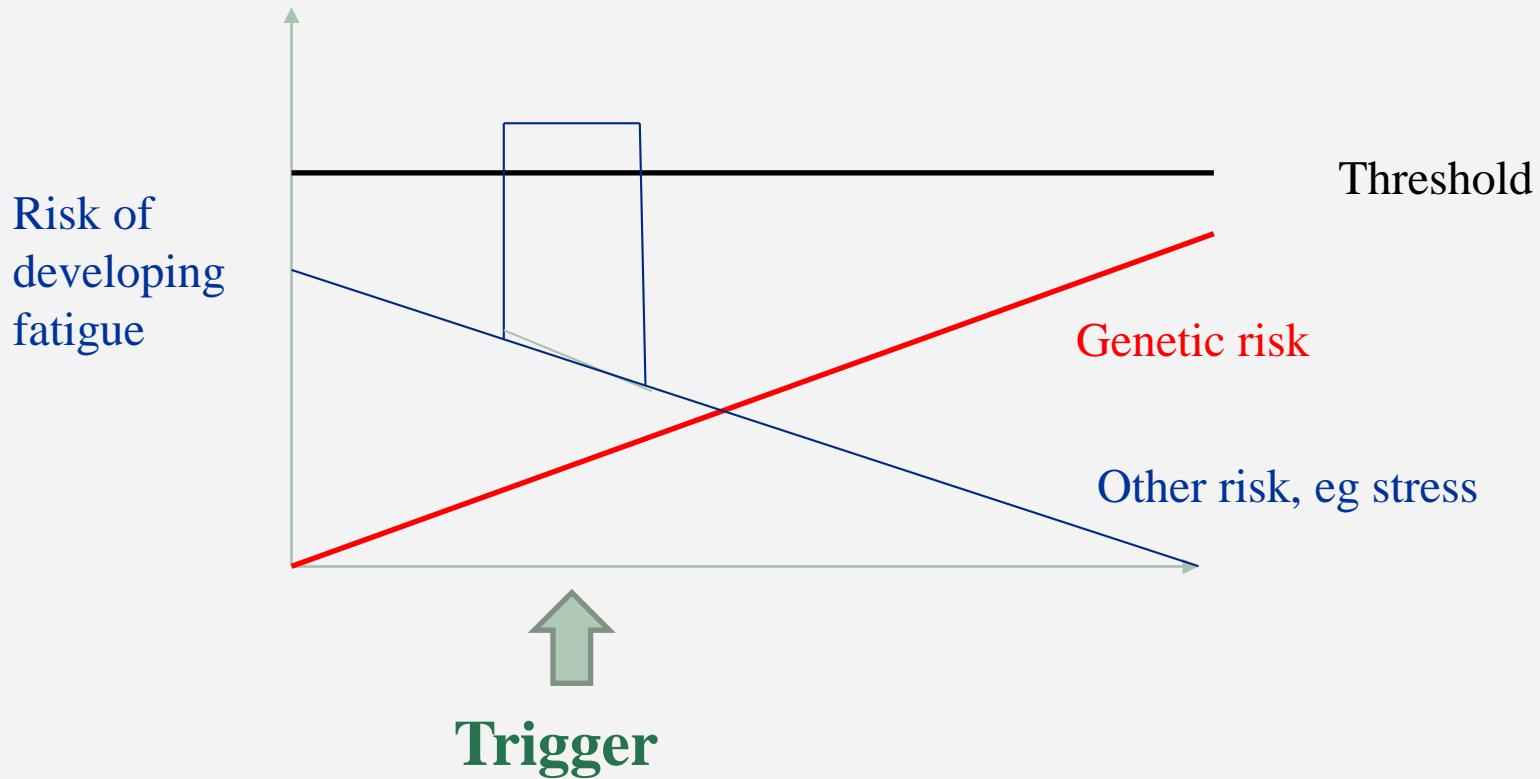
# A model to consider



# A model to consider



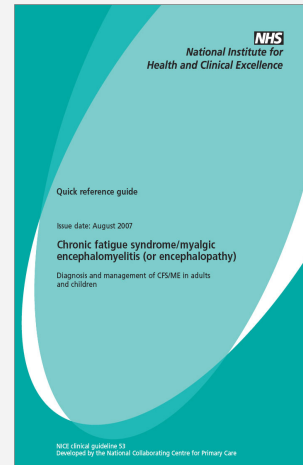
# A model to consider



# What should you do?

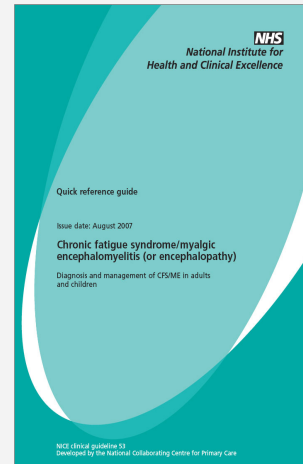
# All Paediatricians

- Make a diagnosis
  - ❖ Exclude other causes
- Treat symptoms
- Provide advice about sleep and activity
- Consider referral to a specialist service



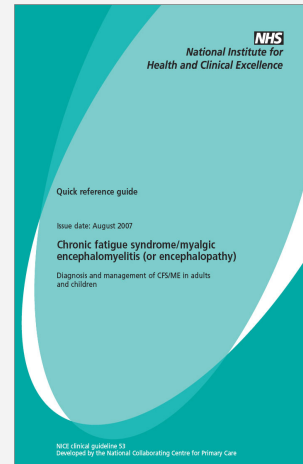
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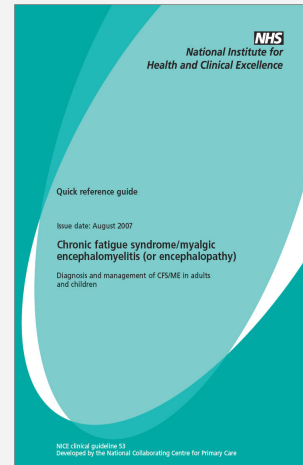
# All Paediatricians

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# All Paediatricians

- Make a diagnosis
  - ❖ Exclude other causes
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# Problems with sleep

- Difficulty getting off to sleep
- Difficulty waking up
- Poor quality sleep
  
- Day night reversal
- Excessive sleeping

# Clinical top tips: sleep

- 1. Don't oversleep
  - ❖ One extra hour ↓ quality



The screenshot shows the NHS Choices website. At the top, the NHS logo is followed by 'choices' in orange and the tagline 'Your health, your choices'. Below this is a navigation bar with three buttons: 'Health A-Z', 'Live Well', and 'Care and support'. The main heading is 'How much sleep do children need?' in green. Below the heading, a paragraph states: 'Below are the approximate hours of sleep needed by children of different ages, as recommended by the Millpond Children's Sleep Clinic.' The first section is '1 week' in green, with a bulleted list: '• daytime: 8 hours' and '• night time: 8 hours 30 minutes'. The second section is '4 weeks' in green.

**NHS choices** Your health, your choices

Health A-Z Live Well Care and support

## How much sleep do children need?

Below are the approximate hours of sleep needed by children of different ages, as recommended by the Millpond Children's Sleep Clinic.

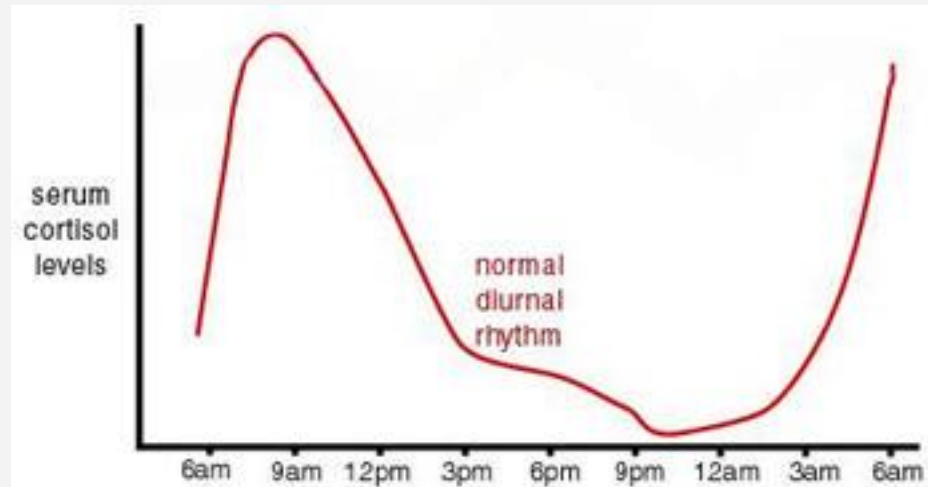
### 1 week

- daytime: 8 hours
- night time: 8 hours 30 minutes

### 4 weeks

# Tip: 2

Anchor wake up time to get cortisol hit in the morning

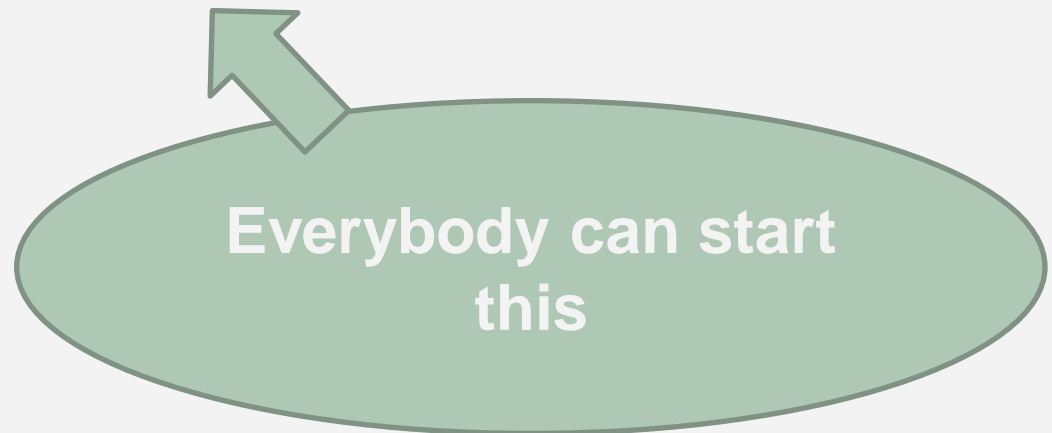


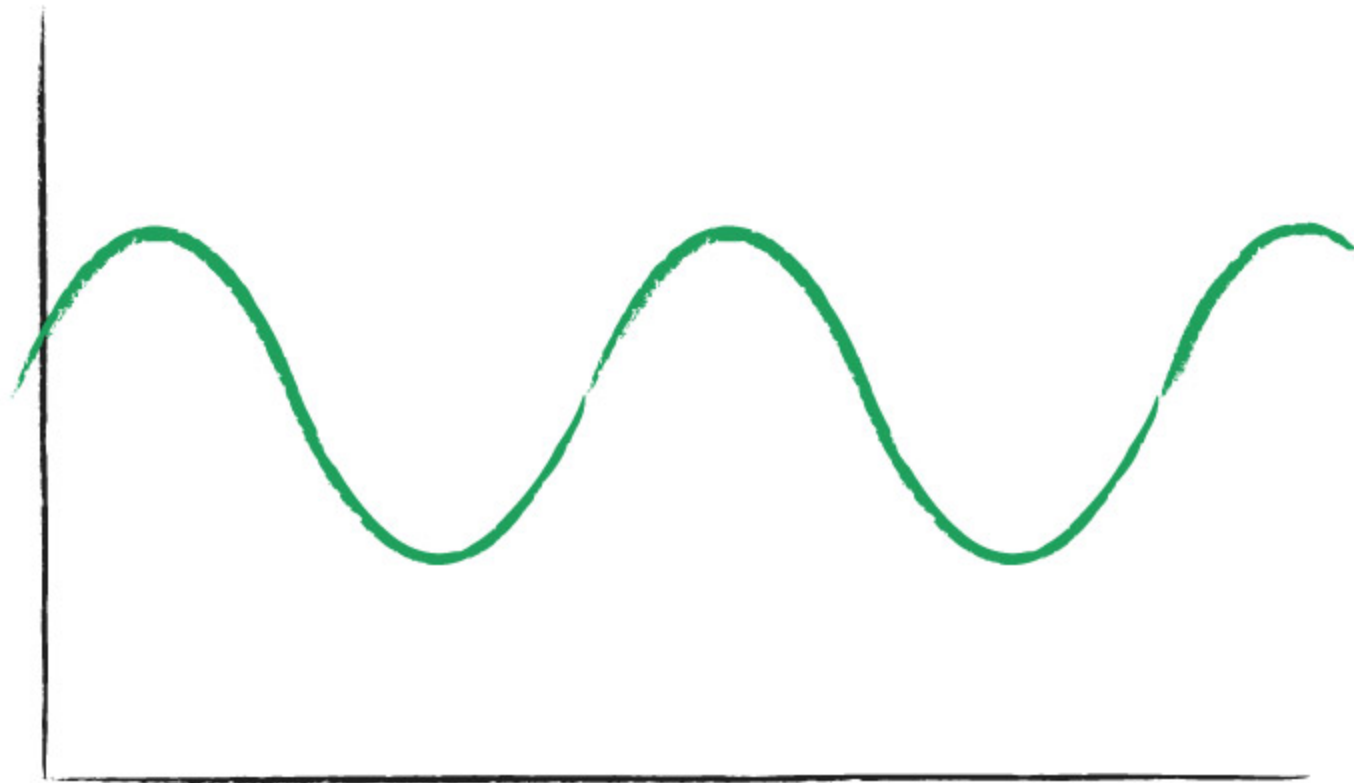
# NICE recommended treatment

- Cognitive Behavioural Therapy
- Graded Exercise Therapy
- Activity Management

# NICE recommended treatment

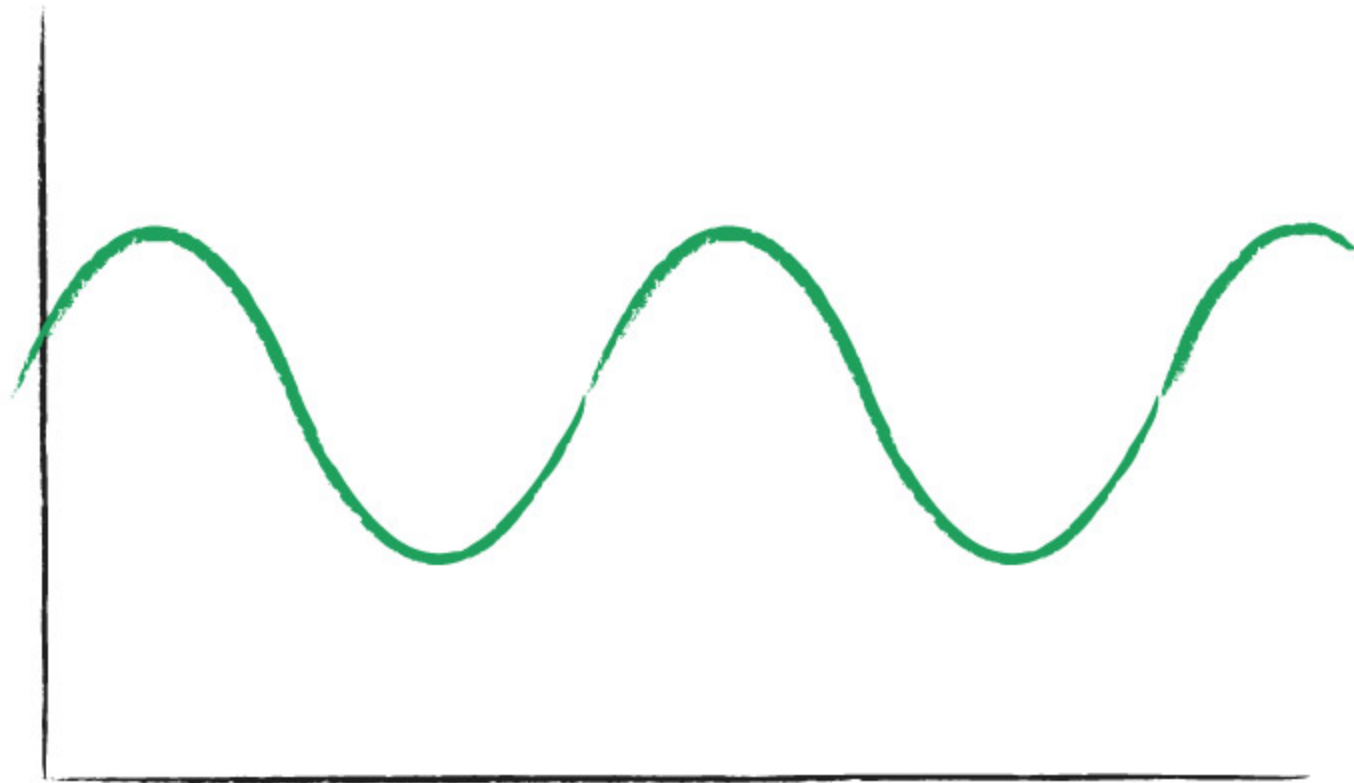
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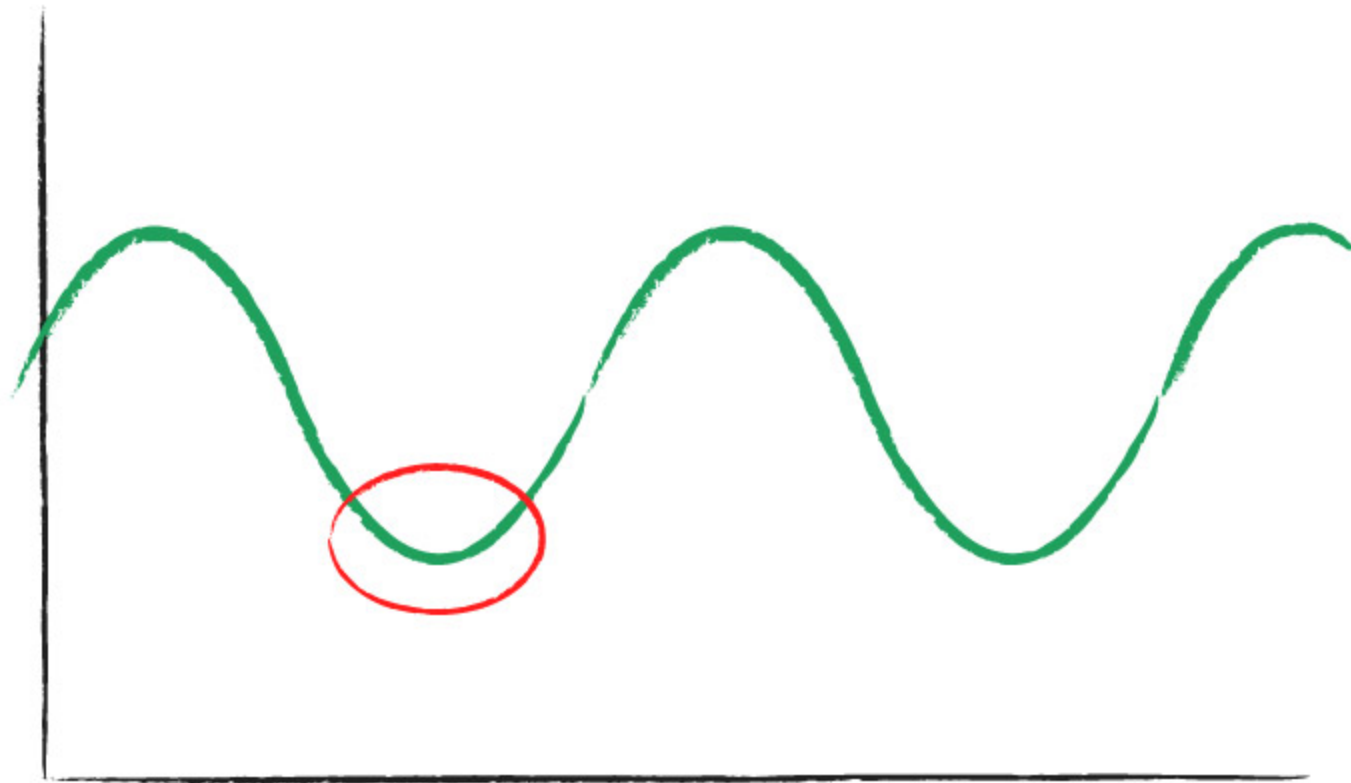


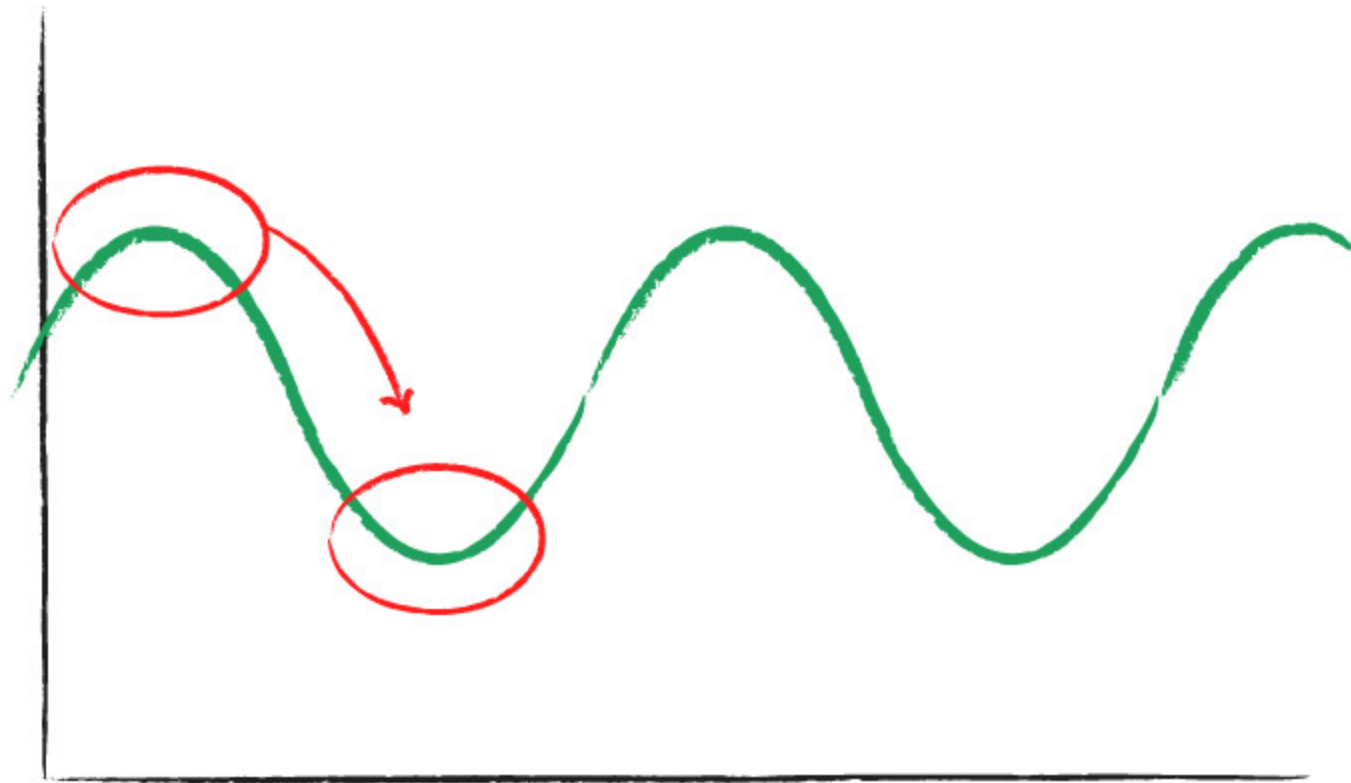
# Activity management

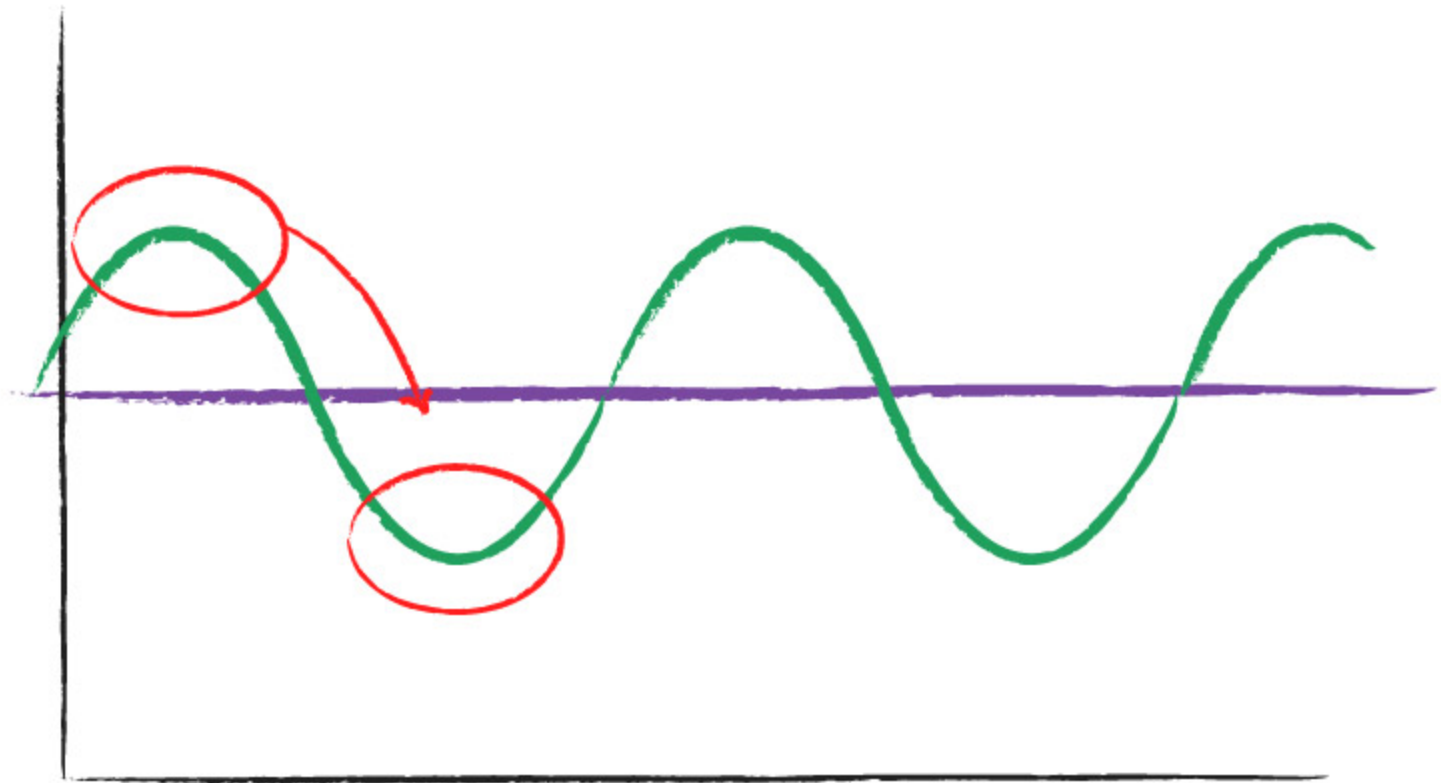
- Boom-Bust versus baseline
- High and low energy
- Rest
- Examples

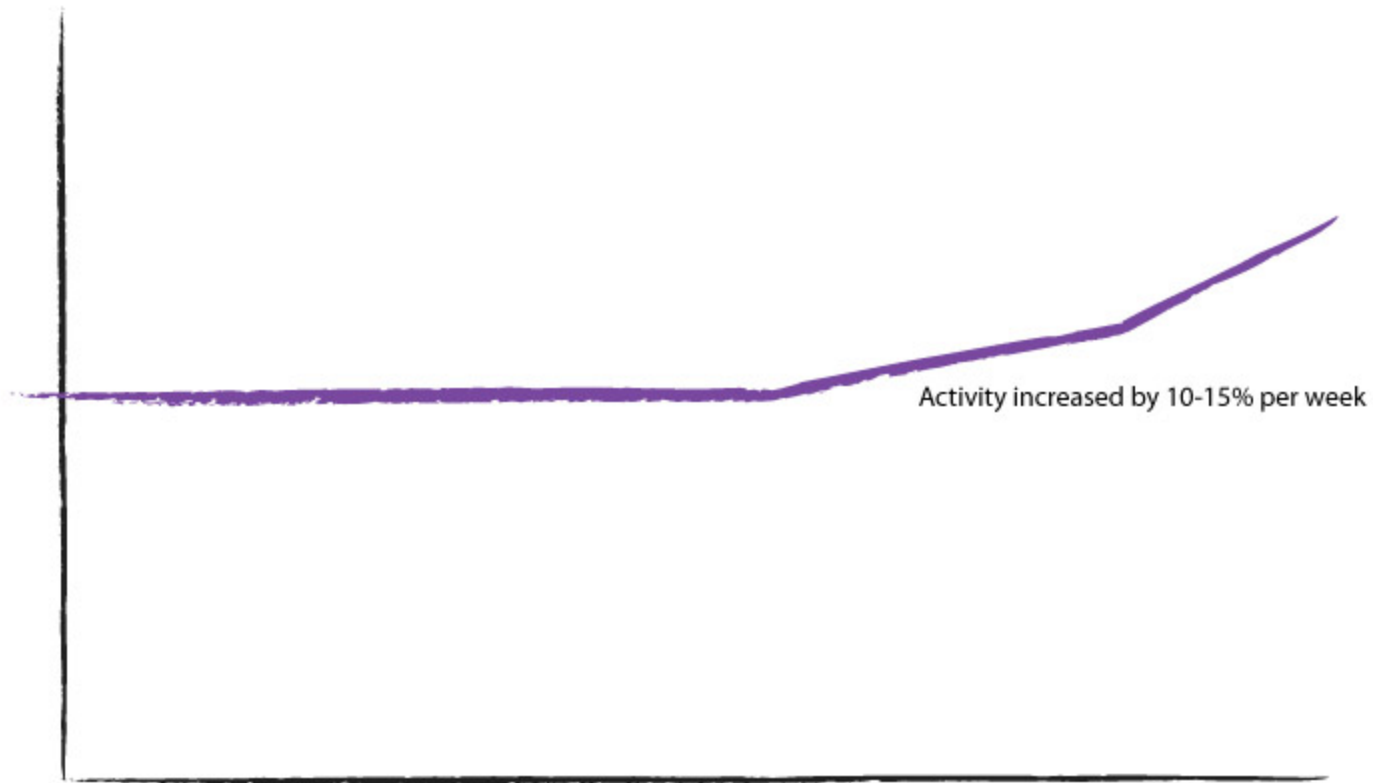












# What is high energy?

- Physical

- ❖ Walking, PE
- ❖ Severely affected - getting out of bed, brushing hair etc

- Cognitive

- ❖ School and home work, Computer, TV if engaged, Reading if difficult

- Emotional

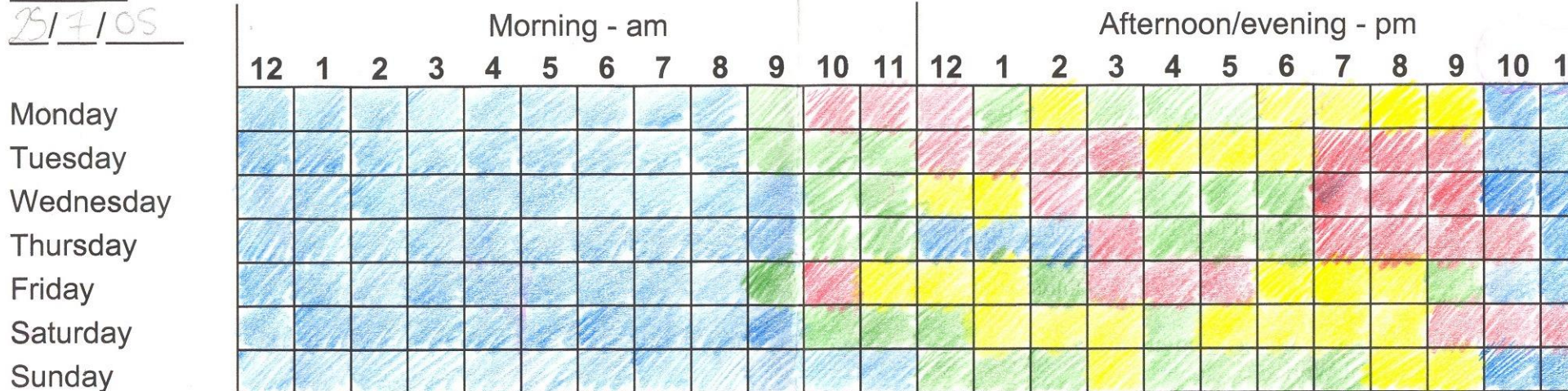
- ❖ Worries, Argument, self talk, Social stuff, Seeing Drs, CBT



# Activity, Rest and Sleep Diary

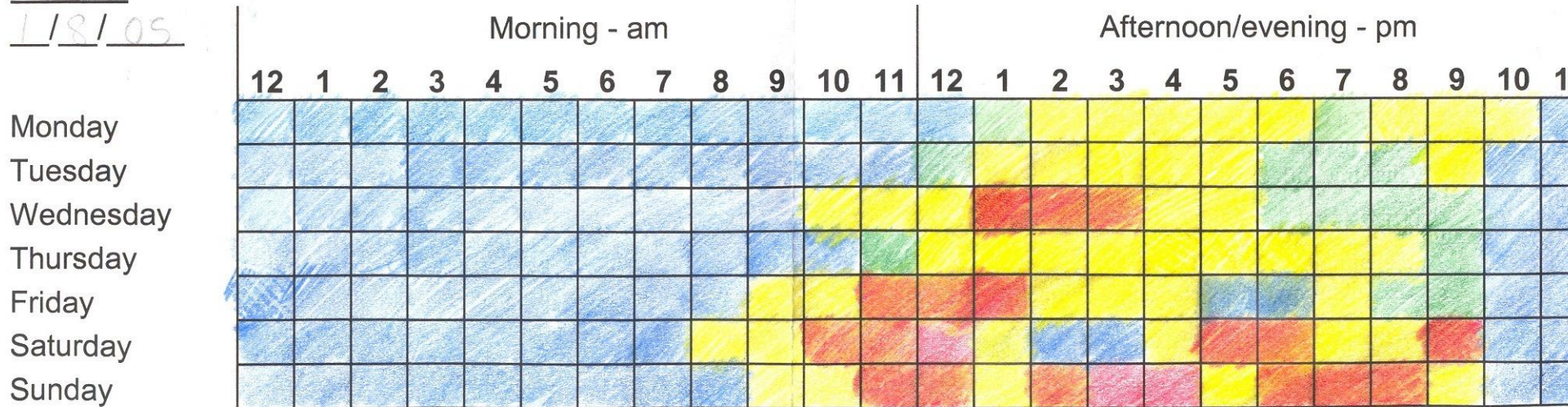
Week 1

25/7/05



Week 2

1/8/05



Key:

 High Energy Activity

 Low Energy Activity

 Rest/ Chill out time

 Sleep

Name:

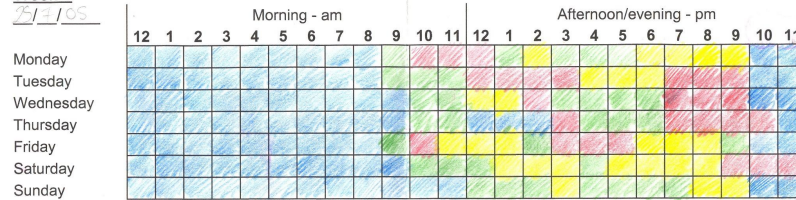


CFS/NHS/PAEDIATRIC  
Activity, Rest and Sleep Diary

NHS

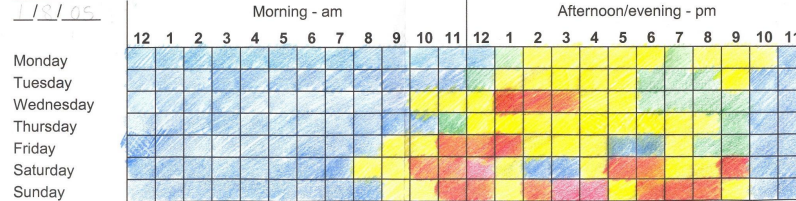
Week 1

21/10/05



Week 2

1/11/05



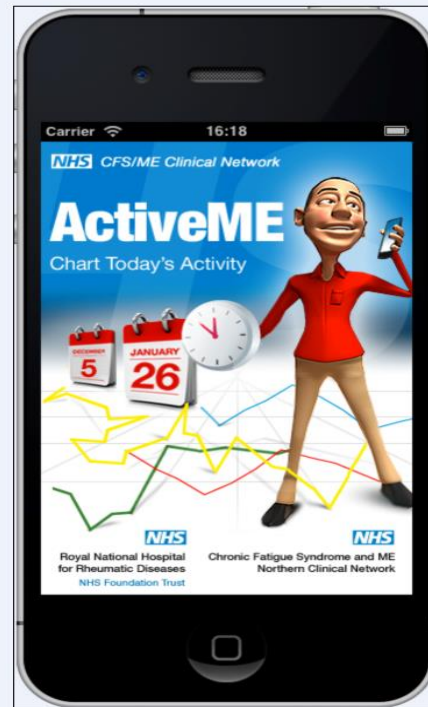
Key: High Energy Activity Low Energy Activity Rest/ Chill out time Sleep

Name:

PAEDIATRIC Activity, Rest + Sleep Diary -> CFS Paediatric



# I Phone App





# What about those with severe pain?

- Make a diagnosis
  - ❖ Are symptoms consistent?
  - ❖ Is there another cause?
- Explain the pathology
- Medication
  - ❖ Amitriptylline, pre-gabalin
- Consider referral to pain service

# Make a diagnosis

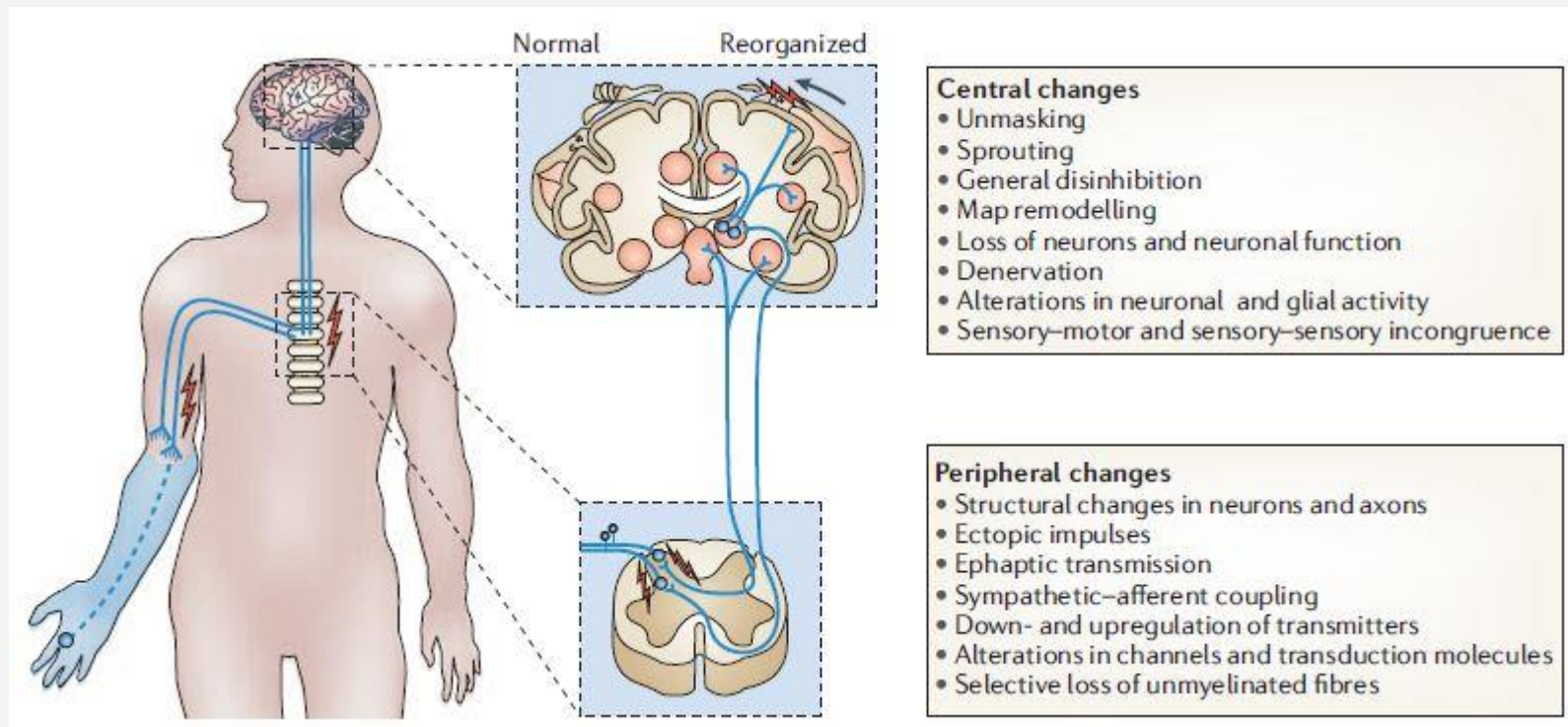
- Chronic disabling pain
- No other explanation
- Pathognomonic symptom
  - ❖ allodynia

# Explain what is happening

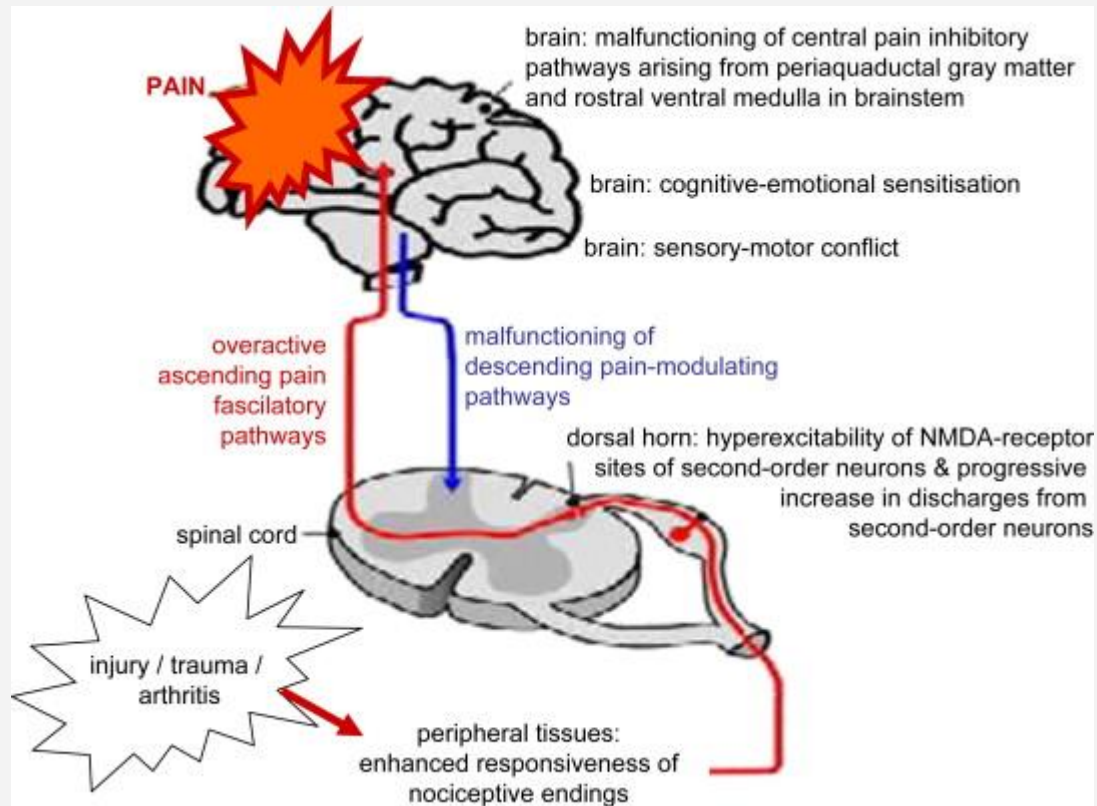
# Explain the pathology

- Phantom limb pain
- Pain pathways
- Brain re-education

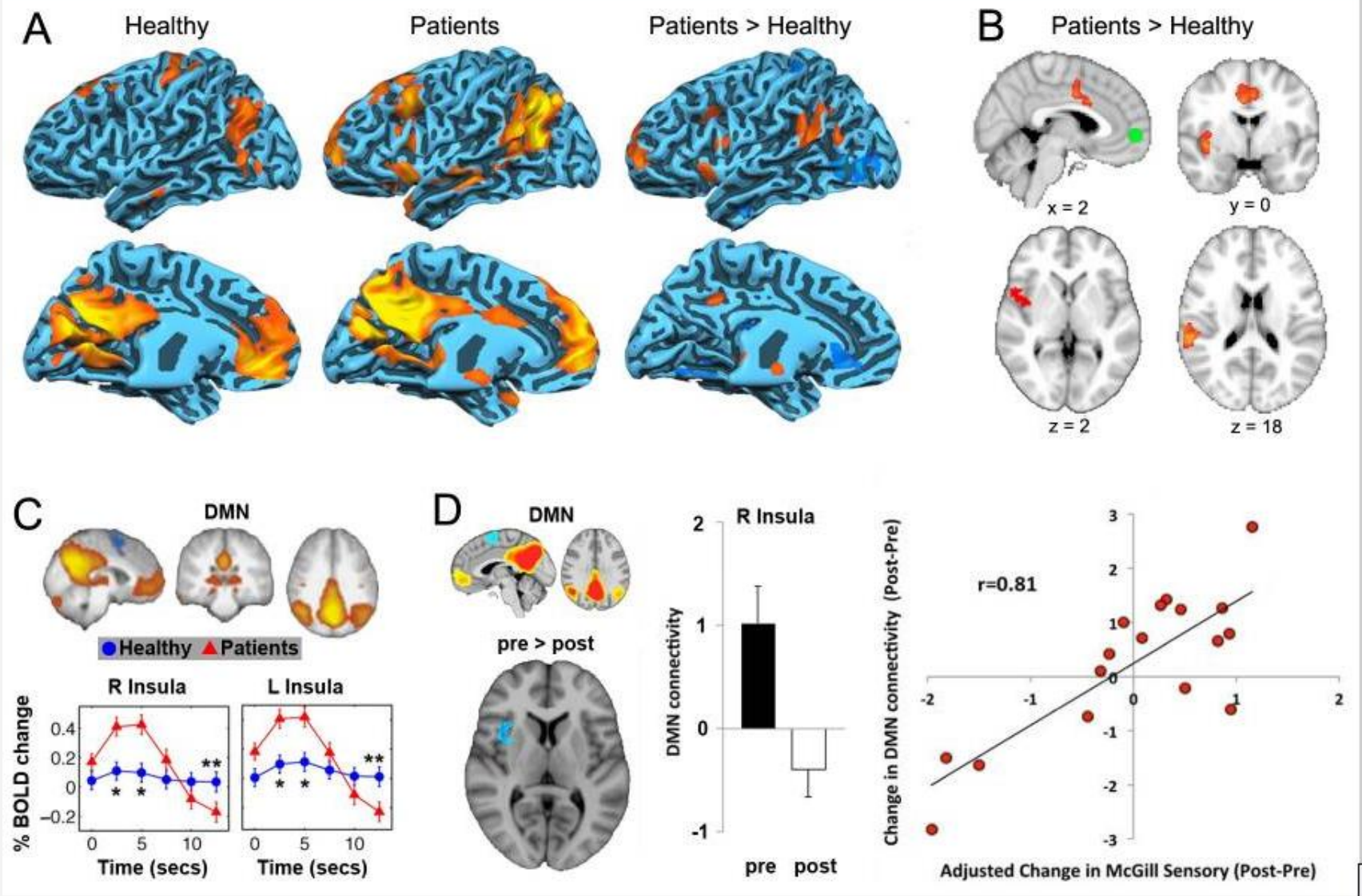
# Phantom Limb Pain



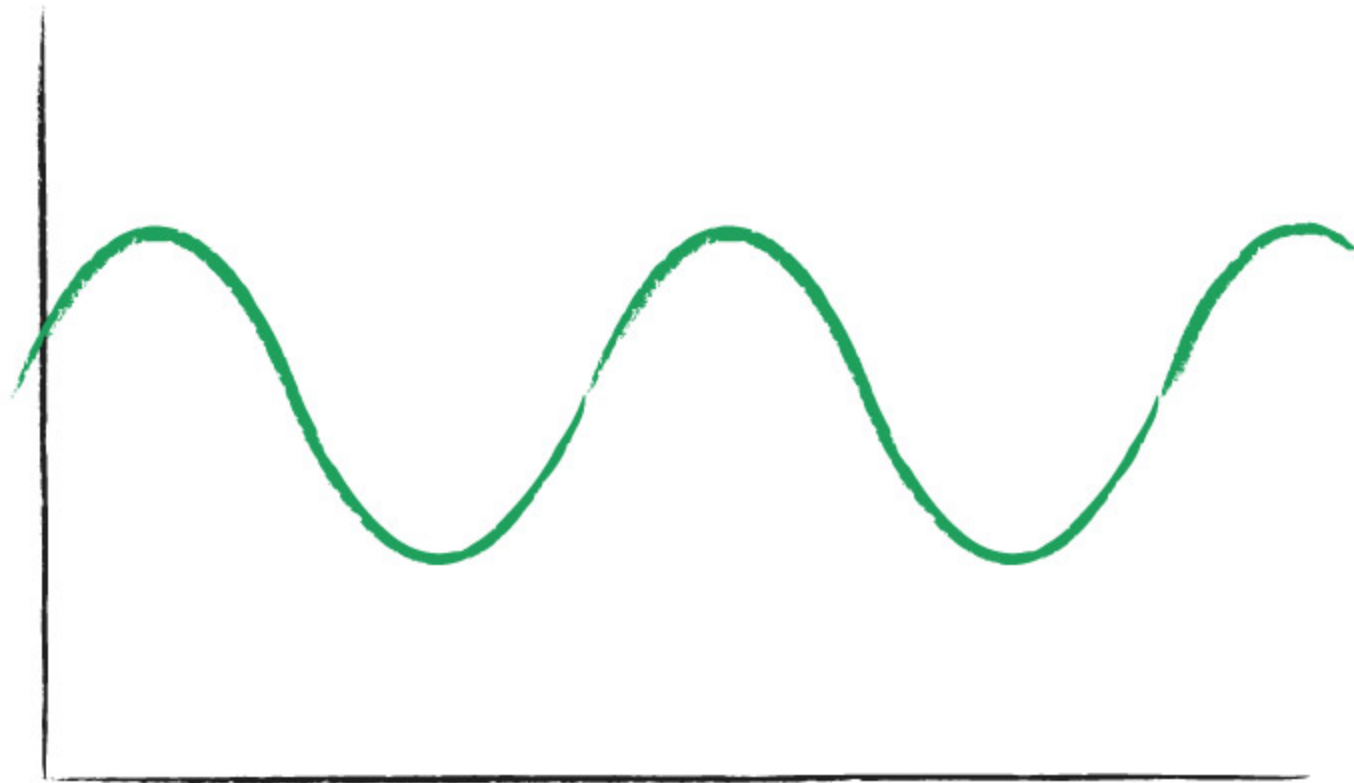
<http://www.completehumanperformance.com/phantom-limb-pain.html>



<http://postgradphysio.files.wordpress.com/2014/01/peripheral-and-central-pain-pathways.jpg>



<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377811/#!po=25.0000>





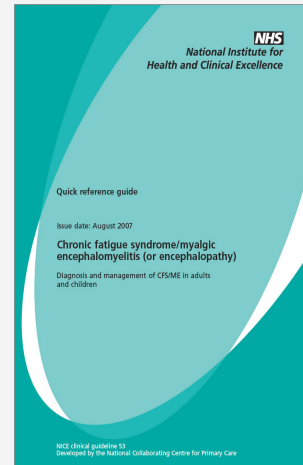
# Treatment

- Explanation
- Activity
- Desensitisation approaches
- Medication
  - amitriptyline, duloxetine, gabapentin or pregabalin
  - Not opioids for children
- Referral to specialist service

<http://www.nice.org.uk/guidance/CG173/chapter/1-Recommendations>

# All Paediatricians

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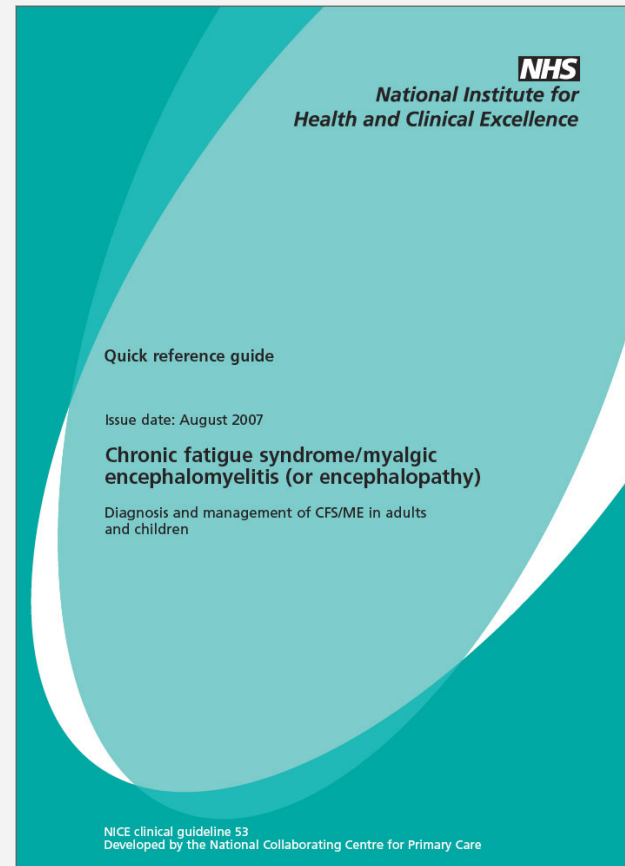


# Accessing specialist care

- Recognition and progress,
  - “And it was a big, such a relief when he got there [CFS/ME Service] ...just to sort of have someone saying ‘Yes, this is what you’ve got’ and this is what you can do”
  - “I found this concrete information that we’ve got from our appointment much, much better”
  - “I think it was really empowering for us to feel we had a form to follow, we had a technique to apply and that really, really helped”

# Specialist treatment

- NICE :
  - ❖ CBT,
  - ❖ GET
  - ❖ Activity Management
- Good evidence for CBT



# Consider particularly for

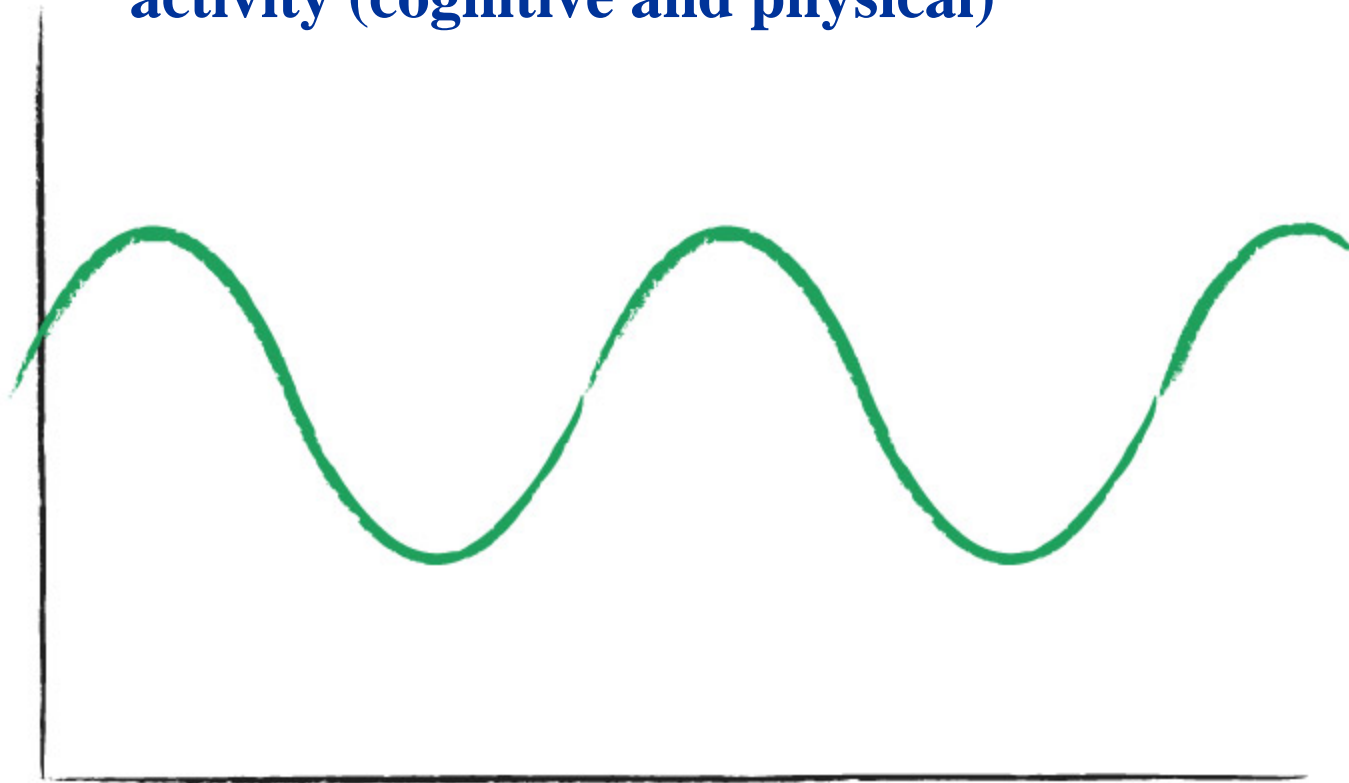
- Primary school children
- Children with significant co-morbid depression and anxiety
- Athletes
- Children with high levels of pain

# What is the difference between AM, GET and CBT?

# What is the difference?

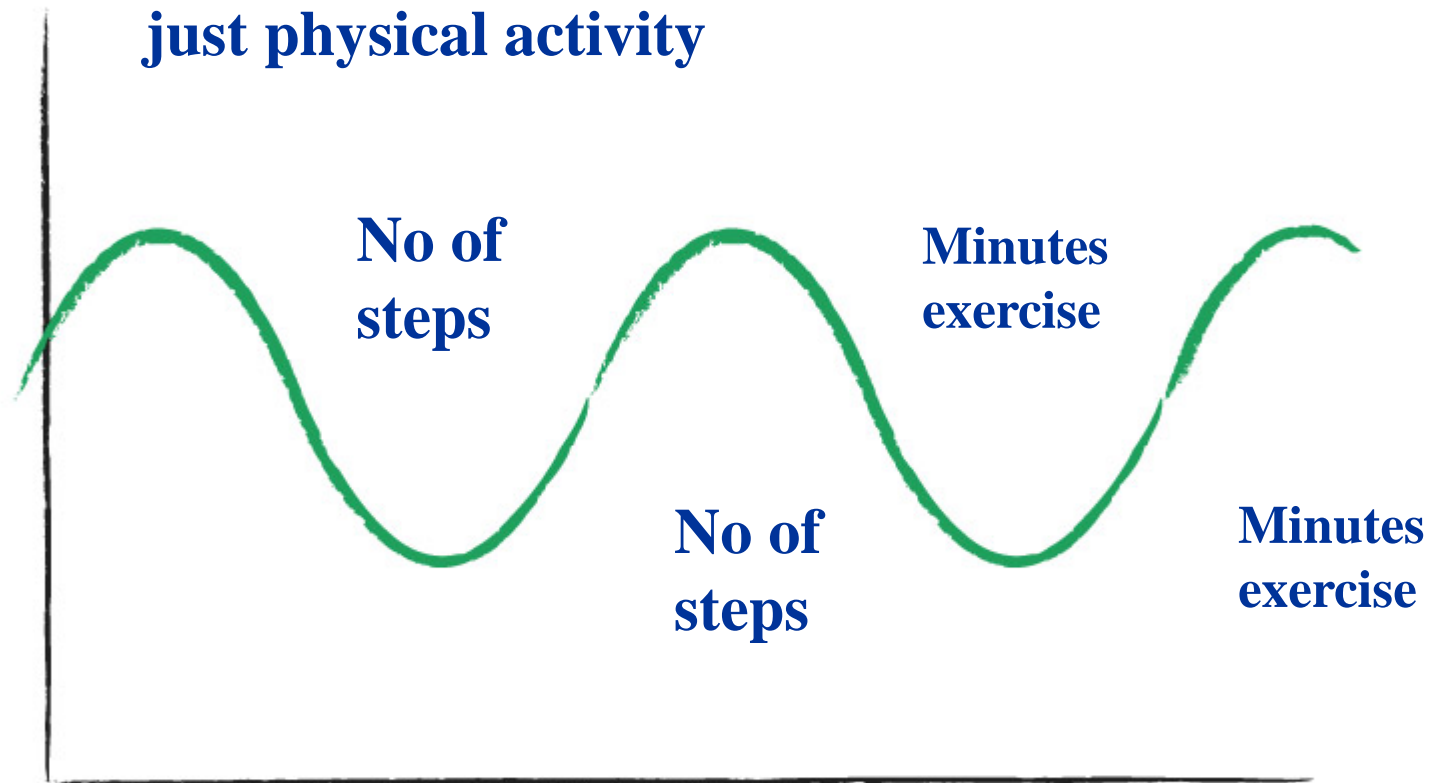
- Behavioural
  - ❖ Activity management
  - ❖ Graded Exercise Therapy
- Cognitive Behavioural Therapy
  - ❖ Behavioural (activity and sleep)
  - ❖ And thoughts

## Activity Management: Behavioural – all activity (cognitive and physical)





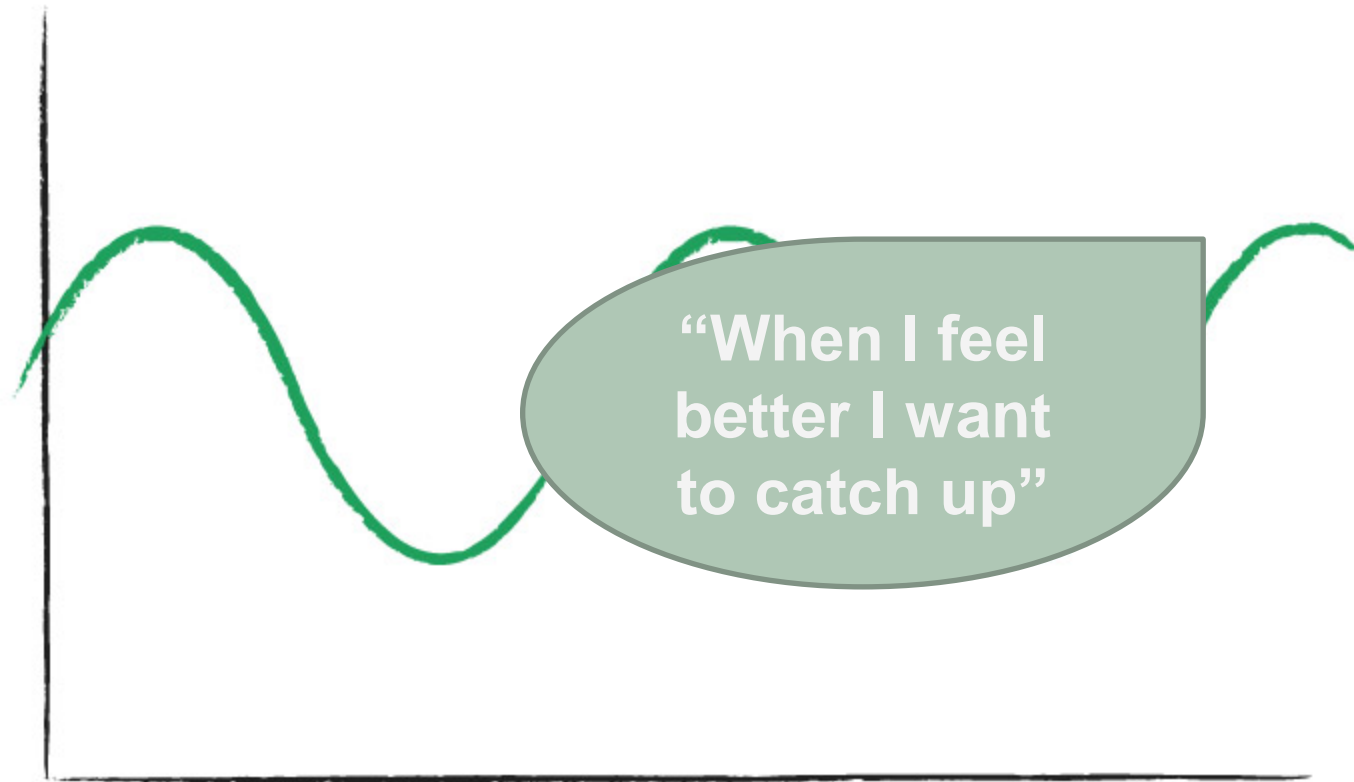
## Graded Exercise Therapy: behavioural – just physical activity



# Cutting back on exercise

- PARTICIPANT 5: I don't like the level.
- MUM 5: No. She wasn't happy.
- PARTICIPANT 5: No, it's not good.
- MUM 5: Ballet is one if YP5's – that's her number one thing that she loves more than anything in life and she's had to cut back a lot on her ballet, which I didn't know they'd say that she had to do and she's really not very happy about it....
- PARTICIPANT 5: No.
- MUM 5: ....to put it mildly.

# CBT



# Do children get better?



- 60% of children recover with specialist treatment at 6 months
- <10% of controls will get better at 6 months



- Less severe children: 3 year natural recovery rates ~ 75%

# In this talk

- A Case
- Making a diagnosis
- What to tell children/families
- Treatment options
  - ❖ What you can do
  - ❖ Specialist treatment
- Questions
- Research updates

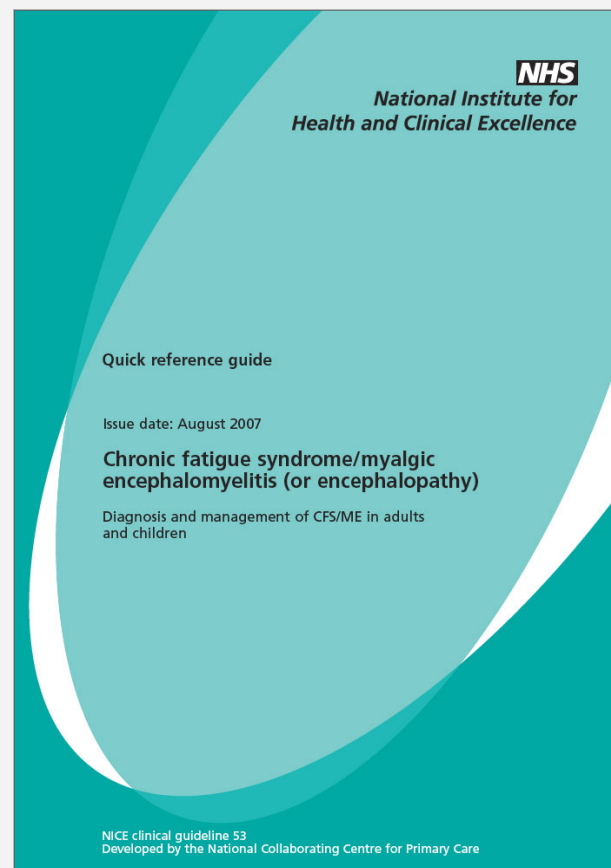


# Some other research updates

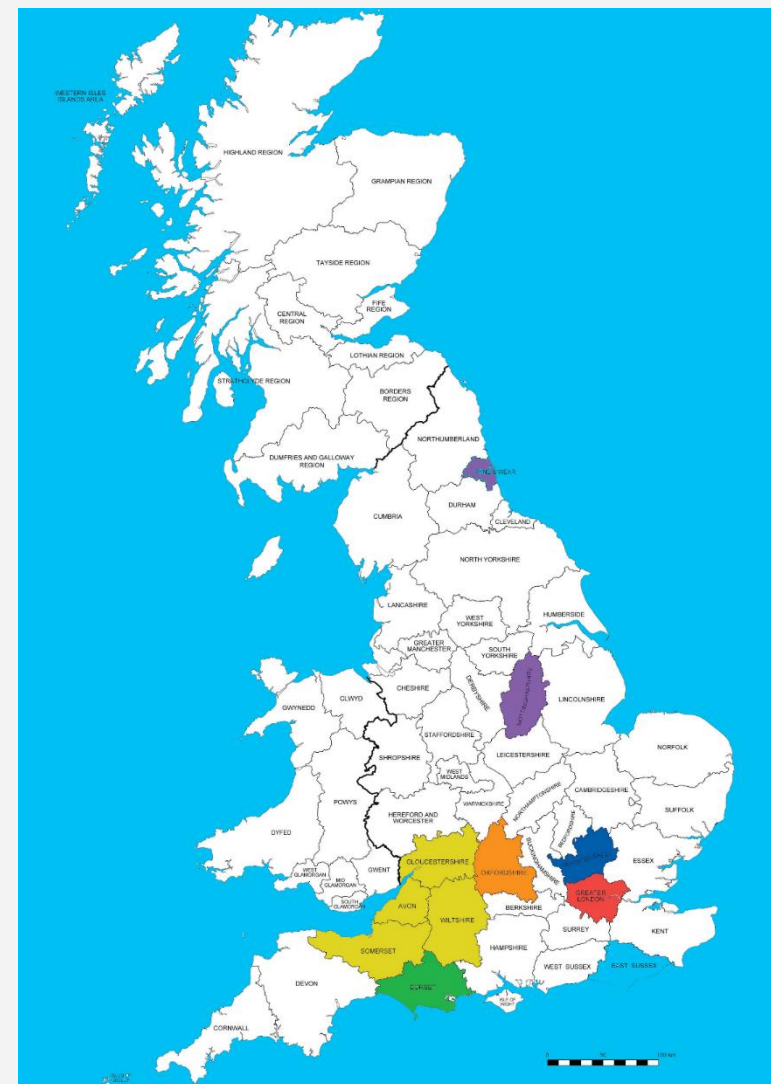
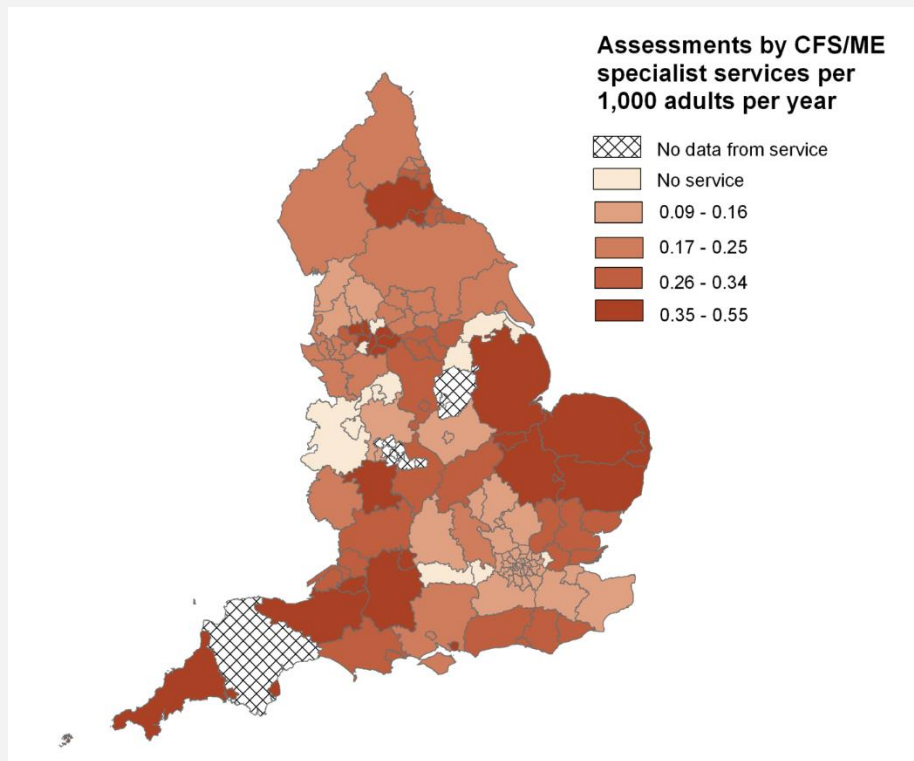
- FITNET-NHS
- SMILE
- Causality

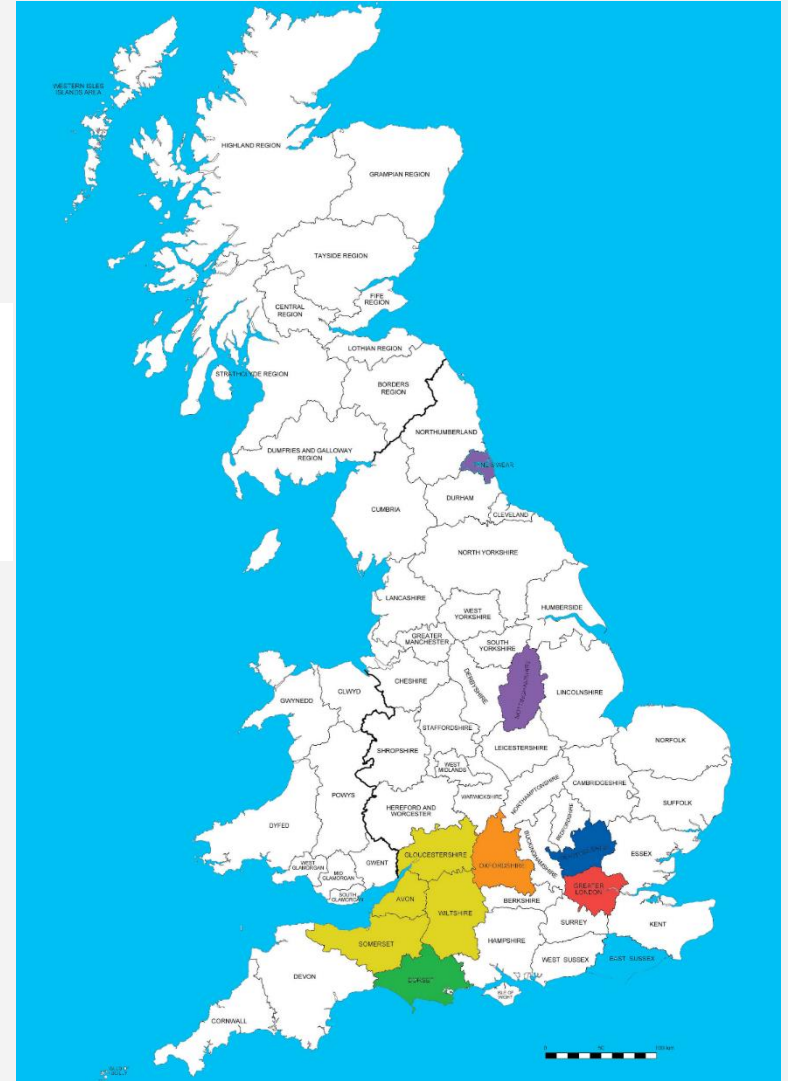
# The problem

- NICE :
  - ❖ CBT,
  - ❖ GET
  - ❖ Activity Management









- 1% secondary school children miss 20% school because of CFS/ME
- Most recover at 6 months with specialist treatment, <10% will recover without
- 90% children with CFS/ME in the UK have no access to local specialist treatment





## Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial

Sanne L Nijhof, Gijs Bleijenberg, Cuno S P M Uiterwaal, Jan L L Kimpen, Elise M van de Putte

### Summary

**Background** Chronic fatigue syndrome is characterised by persistent fatigue and severe disability. Cognitive behavioural therapy seems to be a promising treatment, but its availability is restricted. We developed Fatigue In Teenagers on the interNET (FITNET), the first dedicated internet-based therapeutic program for adolescents with this disorder, and compared its effectiveness with that of usual care.

**Methods** Adolescents aged 12–18 years with chronic fatigue syndrome were assigned to FITNET or usual care in a 1:1 ratio at one tertiary treatment centre in the Netherlands by use of a computer-generated blocked randomisation allocation schedule. The study was open label. Primary outcomes were school attendance, fatigue severity, and physical functioning, and were assessed at 6 months with computerised questionnaires. Analysis was by intention to treat. Thereafter, all patients were offered FITNET if needed. This trial is registered, number ISRCTN59878666.

*Lancet* 2012; 379: 1412–18

Published Online

March 1, 2012

DOI:10.1016/S0140-

6736(12)60025-7

See [Comment](#) page 1372

Department of Paediatrics,  
Wilhelmina Children's Hospital

(S L Nijhof MD,

Prof Jan L L Kimpen PhD,

E M van de Putte PhD), and

Julius Centre for Health



	FITNET (n=67)	Usual care (n=64)	Relative risk (95% CI)	Number needed to treat	p value
<b>Primary outcomes</b>					
Full school attendance*	50 (75%)	10 (16%)	4.8 (2.7–8.9)	1.7	<0.0001
Fatigue severity (CIS-20)†	57 (85%)	17 (27%)	3.2 (2.1–4.9)	1.7	<0.0001
Physical functioning (CHQ-CF87)‡	52 (78%)	13 (20%)	3.8 (2.3–6.3)	1.8	<0.0001
<b>Secondary outcome</b>					
Self-rated improvement§	52 (78%)	17 (27%)	2.9 (1.9–4.5)	2.0	<0.0001
<b>Combined</b>					
Primary outcomes	44 (66%)	5 (8%)	8.4 (3.6–19.8)	1.7	<0.0001
Primary and secondary outcomes	42 (63%)	5 (8%)	8.0 (3.4–19.0)	1.8	<0.0001

Data are number (%), unless otherwise indicated. FITNET=Fatigue In Teenagers on the interNET. CIS-20=checklist individual strength-20. CHQ-CF87=child health questionnaire. \*School absence of 10% or less. †Cutoff score of less than 40. ‡Cutoff score of 85% or more. §Answer “yes” to statement “I have completely recovered” or “I feel much better but still experience some symptoms”.

**Table 3: Recovery at 6 months in FITNET and usual care groups**



- Uses the internet to deliver CBT at home
  - ❖ Individualised therapy with a therapist
  - ❖ Teenagers read information, complete diaries and answer questions on goals, thoughts, feelings during the week
  - ❖ Phone/computer/tablet
  - ❖ Have consultations with the therapist every 1-2 weeks
  - ❖ Consultations are on-line rather than face-to-face

# Randomised to either:



Internet CBT  
Psycho-education  
19 child modules  
19 parent modules

N=367

## Activity Management



Behavioural therapy  
6 Skype calls  
Support for local  
providers

N=367



vodafone UK18:41University of Bristol

fitnetNHS

Fred Bloggslog out

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**AN EXAMPLE – BEN:**

Ben thinks: 'I am certain I have glandular fever. They can't find anything in my blood, but it has to be something like that. The best thing is to rest as much as possible. I will rest and do as little as possible. Otherwise it will only get worse.'

I have glandular fever, I need to rest, otherwise it will get worse

THOUGHTS

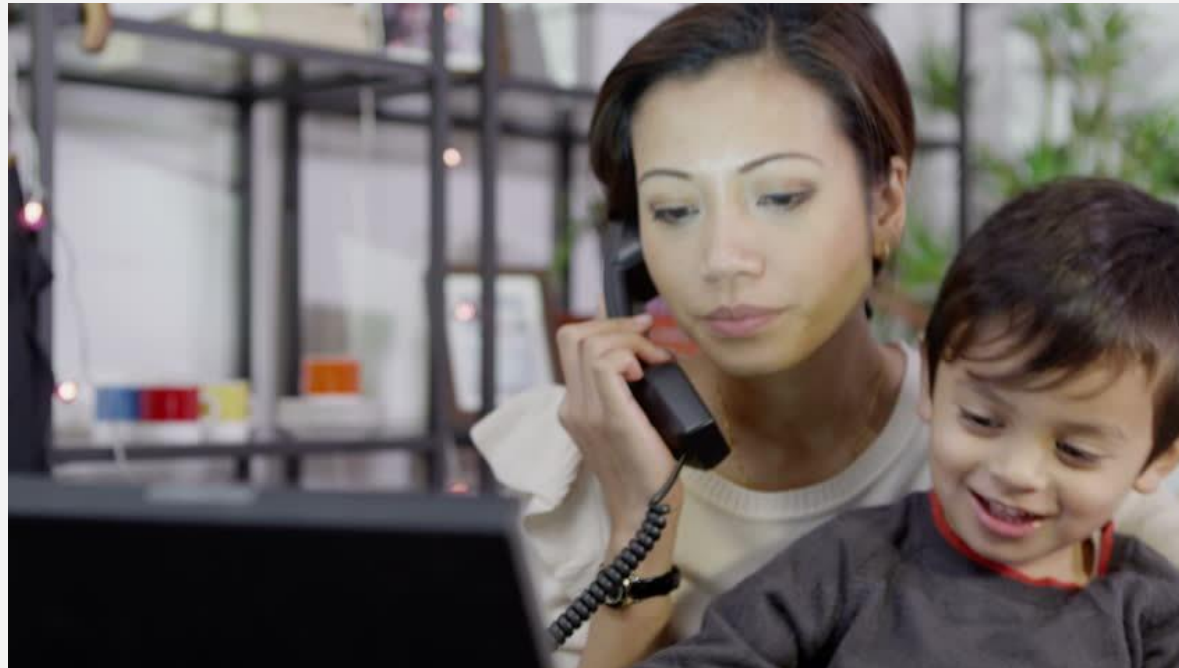
FATIGUE

WHAT YOU DO

**QUESTION:**

What do you think:

1. Will Ben's thoughts help him to get better?





"either way I know I'm gonna get some sort of treatment out of it, some benefit. [...] which is better than nothing " (child)

"I liked the idea of it all being online, I think going to the appointments of different things can be difficult. Whereas this I can just do whenever I fancy." (child)



"I think that was the other thing that kind of attracted me [...] it was like well if it means that she hasn't got to actually go anywhere then yeah obviously that's beneficial" (mother)

Tue, 27 Sep 2016



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Module 1

Module 2

Module 3

Module 4

Module 5

Module 6

Module 7

Module 8

Module 9

Module 10

Module 1 of 19: Getting acquainted

50% complete

Section 1.0 Welcome to FITNET-NHS!

Section 1.1 Information for parents/carers

Section 1.2 Introduction

✓ Section 1.3 Questions about your family

Section 1.4 Questions about school/studies

Section 1.5 What do you do during a regular day?

Section 1.6 Questions about your friends

Section 1.7 Do you have any questions?

## 1.3 Questions about your family

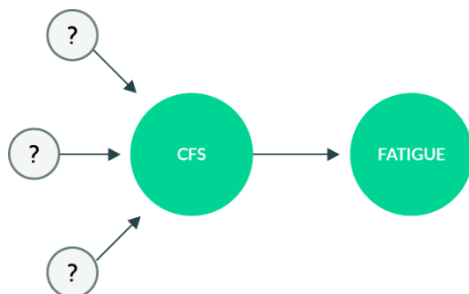
For this task you will answer a number of questions about your family, so that I can get to know you and your family better. Fill in the answers in the fields below the questions.

1. Do you have any siblings?

2. If so, what are their names and how old are they?

3. Do they live at home? Who does, who does not?

## The starting point of CFS/ME is not always this clear



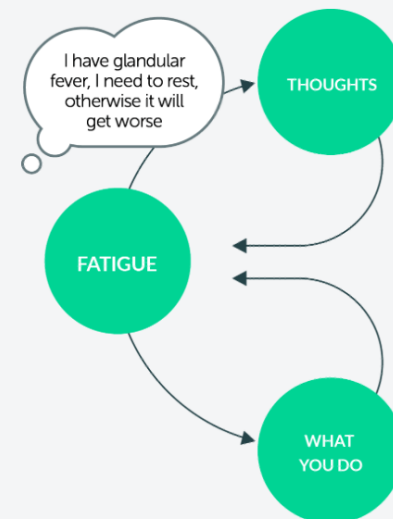
Your doctor has confirmed that you have CFS/ME.

You have been to the doctor because you have been tired for a long while. The doctor has investigated you thoroughly, to check that you do not have another reason for being tired. You have had lots of tests and you do not have anaemia, blood disease, cancer, liver- or kidney disease or intestinal disease. Nothing suggests that you have anything abnormal. Your symptoms also fit with CFS/ME.

It appears that the symptoms associated with CFS/ME often start with a kind of flu, a viral infection. However, the starting point of CFS/ME is not always this clear. Sometimes your

### AN EXAMPLE – BEN:

Ben thinks: 'I am certain I have glandular fever. They can't find anything in my blood, but it has to be something like that. The best thing is to rest as much as possible. I will rest and do as little as possible. Otherwise it will only get worse.'



### QUESTION:

What do you think:

1. Will Ben's thoughts help him to get better?

●●○○ Vodafone UK 18:49

☰ University of Bristol ↻

☰ fitnetNHS Fred Bloggs log out 0

Chapter 1 of 19: Getting a... ✓ Section 1.0 Welcome to I ✓

12% complete

# 1.0 Welcome to FITNET-NHS!

## Introduction

Welcome to FITNET-NHS, a treatment programme for adolescents with Chronic Fatigue Syndrome or Myalgic Encephalomyelitis (CFS/ME). Over the next few weeks, you will start this treatment, which, step by step, will help you work towards recovery. Using this portal, you will keep a diary, answer questions and perform tasks. You will have to do a lot of this yourself, but I will be happy to help you. Go to [My therapist](#) in [Help](#) if you want to know more about me.

## Structure of the treatment

The treatment is made up of chapters. These chapters have sections with information and exercises to do. The first part of

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☰ University of Bristol ↻

☰ fitnetNHS Fred Bloggs log out 0

Chapter 4 of 19: Your goals ✓ Section 4.1 What are you ✓

25% complete

# 4.1 What are you working towards?

The aim of this treatment is to get better. What getting better means, however, differs from person to person. In Chapter 4 you will determine what your goals are for this treatment. What are you trying to achieve?


You are not expected to write down what you want to be when you are older, or what you want to study. Try to write down the concrete things you want to be capable of doing when you recover, as clearly as possible. What do you think are normal activities for someone your age?

WHAT, FOR YOU, ARE THE MOST IMPORTANT THINGS YOU WILL BE ABLE TO DO WHEN YOU ARE HEALTHY AGAIN?

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Tue, 27 Sep 2016



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
## Personal messages

All


Unanswered

Sent


Received

	Subject	From	To	Date
	help	Polly Pocket	Bob Foobar	21 Sep 2016, 8:55 p.m.
	dfddsf	Polly Pocket	Bob Foobar	9 Sep 2016, 11:56 a.m.
	a test message from my Therapist	Bob Foobar	Polly Pocket	6 Sep 2016, 10:09 a.m.
	a test message to my Therapist	Polly Pocket	Bob Foobar	6 Sep 2016, 10:07 a.m.
	test	Polly Pocket	Bob Foobar	6 Sep 2016, 10:07 a.m.

Send Message



Tue, 27 Sep 2016



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log out

Overview

e-consult

Therapist


Treatment

Diaries

Help

My data

My notes

<sup>0</sup>

## Diaries

These diaries are to help you get better. As part of your treatment, your therapist may ask you to fill in particular diaries for short while.

Sleep-wake

To record when you are asleep, lying down to rest or being active.

Goals

To keep track of your overarching goals.

Response to fatigue

To record how you are feeling and what you think about it.

Helpful thoughts

To record all helpful thoughts.

Activities

To record what activities you have been doing.

Missing School

To record the amount of time you spend in school.

Tue, 27 Sep 2016



logged in as  
Polly Pocket

log out

Sleep Wake

Goals

Response To Fatigue

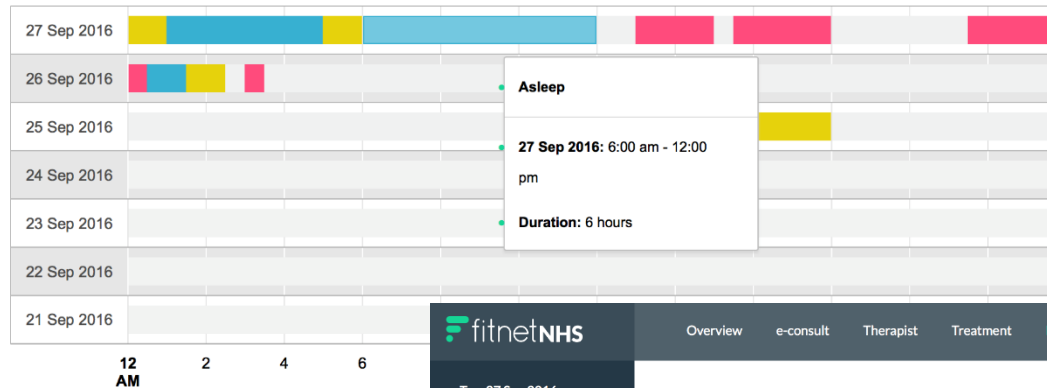
Helpful Thoughts

Activities

Missing School

# Sleep-Wake Cycle

Below you can view your sleep-wake cycle over the past week. You can also make changes for the previous two days.



## Breakdown in minutes

Date Awake Asleep

Tue, 27 Sep 2016



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Polly Pocket

log out

Sleep Wake

Goals

Response To Fatigue

Helpful Thoughts

Activities

Missing School

## Sleep-Wake Cycle -> Edit Entry

Please enter details about your sleep-wake cycle below.

☒ Active
 ☐ Asleep
 ☐ Lying Down

am

12 - 5

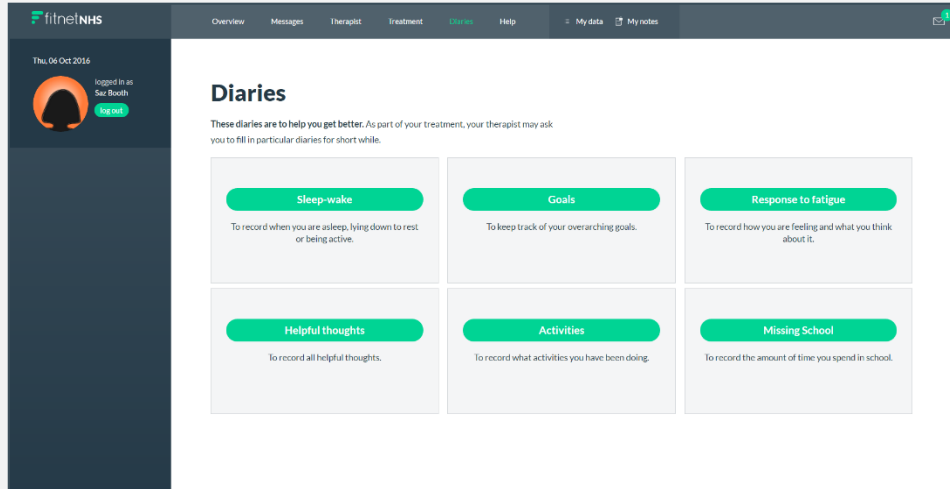
12:00 - 12:30	12:30 - 1:00	1:00 - 1:30	1:30 - 2:00	2:00 - 2:30	2:30 - 3:00
3:00 - 3:30	3:30 - 4:00	4:00 - 4:30	4:30 - 5:00	5:00 - 5:30	5:30 - 6:00

Select all

Clear

6 - 11

# Diaries



**Diaries**

These diaries are to help you get better. As part of your treatment, your therapist may ask you to fill in particular diaries for short while.

- Sleep-wake**  
To record when you are asleep, lying down to rest or being active.
- Goals**  
To keep track of your overarching goals.
- Response to fatigue**  
To record how you are feeling and what you think about it.
- Helpful thoughts**  
To record all helpful thoughts.
- Activities**  
To record what activities you have been doing.
- Missing School**  
To record the amount of time you spend in school.



**Sleep-Wake Cycle -> Add Entry**

Please enter details about your sleep wake cycle below.

am

12-5

6-11

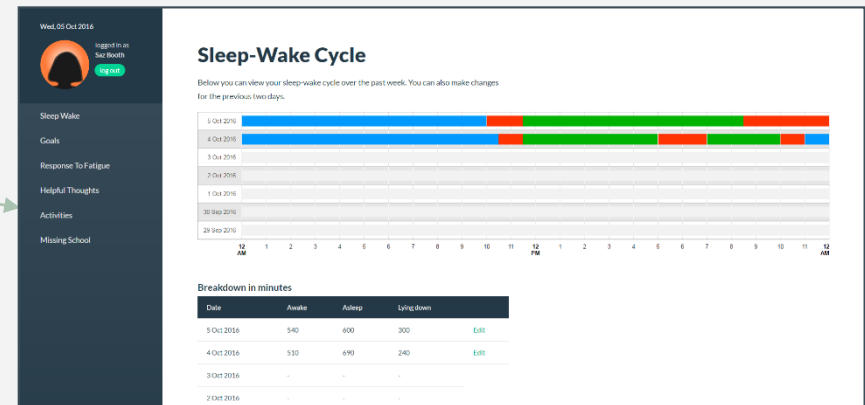
6:00-6:30	6:30-7:00	7:00-7:30	7:30-8:00	8:00-8:30	8:30-9:00
9:00-9:30	9:30-10:00	10:00-10:30	10:30-11:00	11:00-11:30	11:30-12:00

Select all Clear

pm

12-5

6-11



**Sleep-Wake Cycle**

Below you can view your sleep-wake cycle over the past week. You can also make changes for the previous two days.

Date	Awake	Asleep	Lying down	Edit
5 Oct 2016	540	600	300	Edit
4 Oct 2016	510	690	240	Edit
3 Oct 2016	-	-	-	-
2 Oct 2016	-	-	-	-

# What will we find out?

- Can we deliver treatment throughout the UK?
- What do parents think about treatment?
- What do teenagers think about treatment?
- Does it work?
- Does it work for teenagers with CFS/ME and depression or anxiety?
- Is it good value for money?







# Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial

Esther M Crawley,<sup>1</sup> Daisy M Gaunt,<sup>2,3</sup> Kirsty Garfield,<sup>2,3</sup> William Hollingworth,<sup>2</sup> Jonathan A C Sterne,<sup>2</sup> Lucy Beasant,<sup>1</sup> Simon M Collin,<sup>1</sup> Nicola Mills,<sup>2</sup> Alan A Montgomery<sup>3,4</sup>



## What is already known on this topic?

- ▶ Paediatric chronic fatigue syndrome (CFS)/ myalgic encephalitis (ME) is relatively common with a negative impact on school, mood and quality of life.
- ▶ Even with effective treatment, a significant number of children have not recovered at 6 months.
- ▶ The Lightning Process (LP) is used by children with CFS/ME in the UK but with no evidence of effectiveness.

## What this study adds?

- ▶ At 6 months, children who received LP in addition to SMC had better physical function, fatigue and less anxiety.
- ▶ At 12 months, children who received LP in addition to SMC had better fatigue, anxiety, depression and school attendance.
- ▶ Adding LP is probably cost-effective but not all children wish to take part.

**Table 2** Primary outcome

SF-36 physical function	SMC group		SMC plus LP group		Crude difference in means (95% CI), p value	Adjusted difference in means* (95% CI), p value		Adjusted difference in means† (95% CI), p value	N
	Mean	N	Mean	N					
Baseline	56.0	49	53.0	50					
6 months (primary outcome)‡	70.2	37	81.7	45	11.5 (3.1 to 19.8), 0.008	12.5 (4.5 to 20.5), 0.003	81	12.9 (3.6 to 22.1), 0.007	76
Children recruited from 1 February 2011	70.5	34	81.4	39	10.9 (1.8 to 20.0), 0.020	11.8 (3.2 to 20.3), 0.008	72	13.1 (3.3 to 22.8), 0.009	68
With imputation of missing data	70.9	49	81.1	51	10.2 (2.2 to 18.2), 0.013	11.3 (3.8 to 18.9), 0.004	100	11.8 (3.6 to 19.9), 0.005	100
Effect among compliers (CACE)					15.2 (5.0 to 25.3), 0.003	16.6 (6.9 to 26.2), 0.001	81	17.5 (7.1 to 28.0), 0.001	76
12 months‡	71.8	38	86.1	42	14.2 (4.6 to 23.8), 0.004	15.1 (5.8 to 24.4), 0.002	79	16.4 (6.1 to 26.8), 0.002	73
With imputation of missing data	73.1	49	85.5	51	12.4 (3.3 to 21.5), 0.008	12.6 (4.0 to 21.3), 0.005	100	14.7 (5.6 to 23.9), 0.002	100
Effect among compliers (CACE)					16.2 (5.6 to 26.7), 0.003	17.1 (7.0 to 27.3), 0.001	79	18.6 (6.9 to 30.4), 0.002	73
Average of 3, 6 and 12 month differences§						13.6 (6.7 to 20.4), <0.001	90	13.5 (6.0 to 21.0), <0.001	84
Average of 6 and 12 month differences§						14.4 (7.3 to 21.5), <0.001	87	14.9 (7.0 to 22.7), <0.001	81

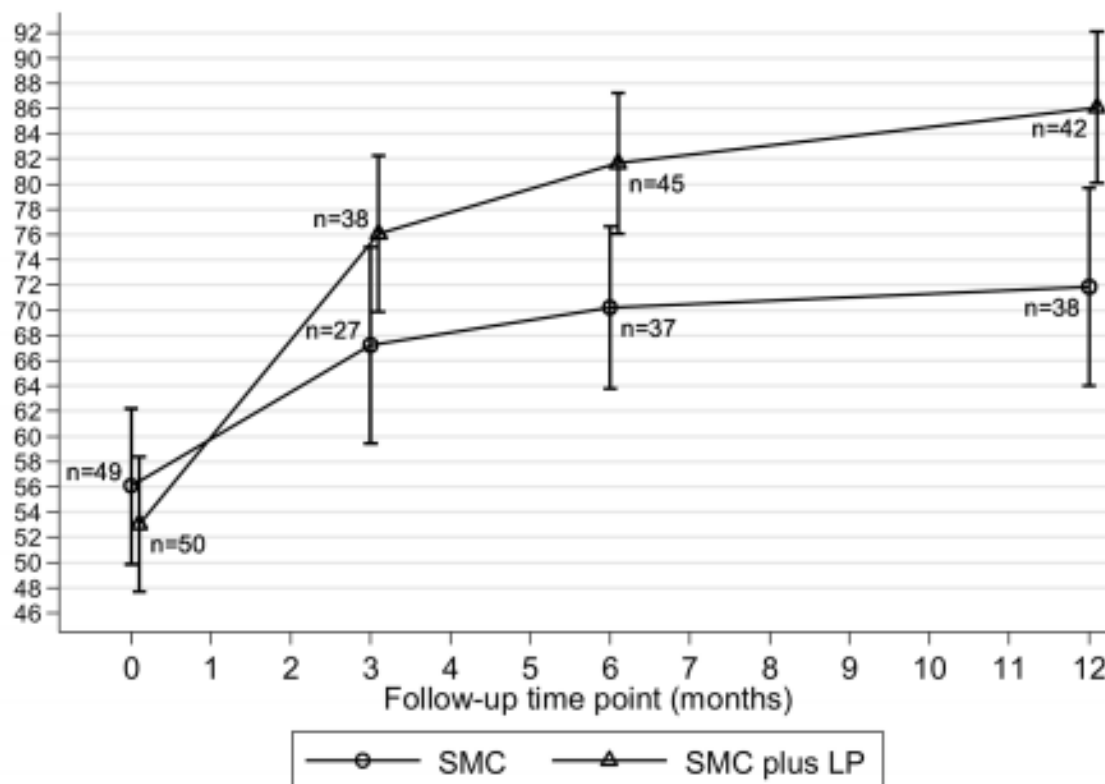
\*Adjusted for age, gender and baseline outcome.

†Adjusted for age, gender, baseline outcome, baseline Spence Children's Anxiety Scale and Visual Analogue Scale.

‡Higher score=fewer symptoms, better function.

§Based on a repeated measures analysis that was additionally adjusted for time point as a categorical variable.

CACE, Complier Average Causal Effect; LP, Lightning Process; SF-36, the 36-Item Short-Form Health Survey; SMC, specialist medical care.



Error bars are 95% Confidence Intervals.

**Figure 2** Mean SF36 physical function over time. LP, Lightning Process; SF-36, the 36-Item Short-Form Health Survey; SMC, specialist medical care.

Crawley EM, et al. *Arch Dis Child* 2017;0:1–10. doi:10.1136/archdischild-2017-313375

Table 3 Secondary outcomes

	SMC group		SMC plus LP group		Crude difference in means (95% CI), p value	Adjusted difference in means* (95% CI), p value		Adjusted difference in means† (95% CI), p value	N
	Mean	N	Mean	N					
Chalder Fatigue score 6 months‡	19.8	37	14.4	44	-5.4 (-8.6 to 2.1), 0.001	-4.7 (-7.9 to 1.6), 0.003	80	-5.4 (-8.9 to 1.9), 0.003	76
Chalder Fatigue score 12 months‡	15.7	38	12.3	42	-3.4 (-6.6 to 0.1), 0.041	-3.2 (-6.3 to 0.1), 0.045	79	-4.0 (-7.2 to 0.7), 0.017	74
Pain VAS 6 months‡	32.8	28	23.4	33	-9.5 (-23.5 to 4.6), 0.183	-11.3 (-23.0 to 0.3), 0.057	58	-9.3 (-21.1 to 2.6), 0.124	58
Pain VAS 12 months‡	32.0	27	21.8	32	-10.2 (-24.6 to 4.2), 0.161	-9.4 (-21.5 to 2.7), 0.125	56	-6.5 (-19.4 to 6.5), 0.321	54
SCAS 6 months‡	37.4	28	24.7	33	-12.7 (-22.0 to 3.3), 0.009	-8.7 (-16.9 to 0.5), 0.039	61	-10.0 (-18.5 to 1.5), 0.022	58
SCAS 12 months‡	36.3	27	19.6	31	-16.7 (-25.9 to 7.5), 0.001	-12.1 (-20.1 to 4.1), 0.004	56	-14.5 (-22.4 to 6.7), <0.001	52
HADS anxiety score 6 months‡	9.7	28	6.1	33	-3.7 (-6.0 to 1.3), 0.003	-3.3 (-5.6 to 1.0), 0.005	60	-3.5 (-5.6 to 1.5), 0.001	57
HADS anxiety score 12 months‡	8.3	27	5.3	33	-3.1 (-5.2 to 0.9), 0.006	-2.8 (-4.7 to 0.8), 0.006	59	-2.6 (-4.7 to 0.4), 0.019	53
HADS depression score 6 months‡	5.9	28	4.2	33	-1.7 (-4.0 to 0.6), 0.141	-1.6 (-3.9 to 0.7), 0.161	59	-1.5 (-3.5 to 0.5), 0.129	57
HADS depression score 12 months‡	4.6	27	2.8	33	-1.9 (-3.6 to 0.2), 0.033	-1.7 (-3.3 to 0.2), 0.030	58	-1.8 (-3.4 to 0.1), 0.037	53
School/college attendance in the previous week 6 months§ (days)	2.6	37	3.2	41	0.7 (-0.1 to 1.4), 0.083	0.7 (0.0 to 1.4), 0.064	77	0.6 (-0.2 to 1.4), 0.135	72
School/college attendance in the previous week 12 months§ (days)	3.1	36	4.1	34	1.0 (0.2 to 1.7), 0.010	0.9 (0.2 to 1.6), 0.018	69	1.0 (0.2 to 1.8), 0.012	65

\*Adjusted for age, gender and baseline outcome.

†Higher score=more symptoms, poorer function.

‡Adjusted for age, gender, baseline outcome, baseline SCAS and VAS (as appropriate).

§Higher score=fewer symptoms, better function.

HADS, Hospital Anxiety and Depression Scale; LP, Lightning Process; SCAS, Spence Children's Anxiety Scale; SF-36: The 36-Item Short-Form Health survey; SMC, specialist medical care; VAS, Visual Analogue Scale.

**Table 4** MI and complete case analysis of total HC+LP costs and QALYs and NMB (£20 k) at 6 and 12 months; by treatment group, all adjusted for baseline value, age, sex, baseline SCAS and baseline VAS

	SMC			SMC plus LP			Incremental difference	
	Mean	(SE)	n	Mean	(SE)	n	(95% CI)	n
6-month complete case								
Total cost (£)	942	(89)	13	1563	(127)	21	621 (323 to 919)	34
QALYs	0.252	(0.021)	22	0.259	(0.016)	32	0.008 (−0.057 to 0.073)	34
NMB at £20 000 per QALY	4225	(578)	13	3762	(461)	21	−464 (−1852 to 925)	34
6-month imputed								
Total cost (£)	1123	(66)	49	1517	(54)	51	394 (236 to 553)	100
QALYs	0.247	(0.015)	49	0.274	(0.014)	51	0.026 (−0.015 to 0.068)	100
NMB at £20 000 per QALY	3819	(328)	49	3954	(276)	51	135 (−733 to 1003)	100
12-month complete case								
Total cost (£)	1369	(160)	11	1814	(211)	16	445 (−57 to 947)	27
QALYs	0.551	(0.039)	21	0.597	(0.032)	30	0.080 (−0.064 to 0.225)	27
NMB at £20 000 per QALY	9454	(1202)	11	10615	(1113)	16	1161 (−1966 to 4289)	27
12-month imputed								
Total cost (£)	1612	(84)	49	2002	(67)	51	390 (189 to 591)	100
QALYs	0.533	(0.025)	49	0.628	(0.021)	51	0.095 (0.030 to 0.160)	100
NMB at £20 000 per QALY	9042	(521)	49	10551	(427)	51	1508 (148 to 2869)	100

HC, health care; LP, Lightning Process; MI, multiple imputation; NMB, net monetary benefit; QALY, quality-adjusted life years; SCAS, Spence Children's Anxiety Scale; SMC, specialist medical care; VAS, Visual Analogue Scale.

# What increases your risk of getting CFS/ME?

Its complicated!

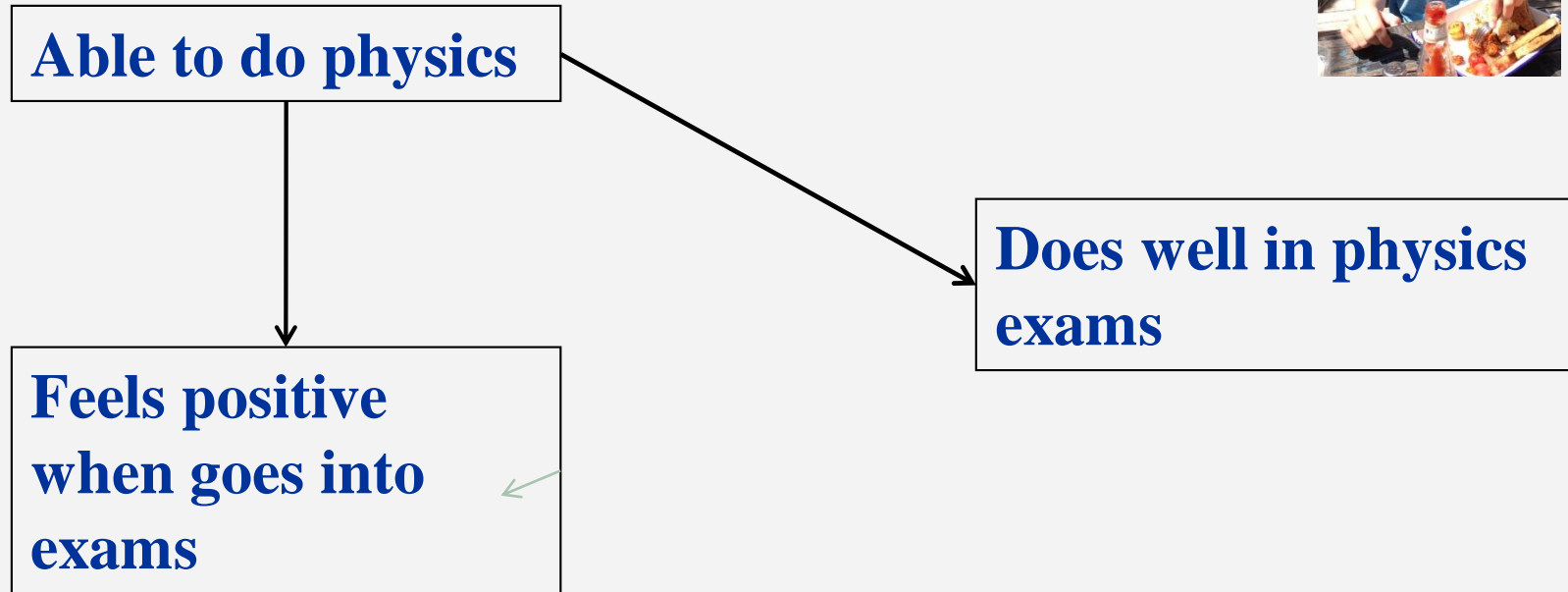
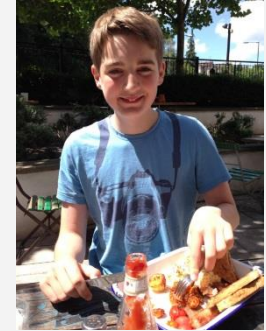
# Its complicated

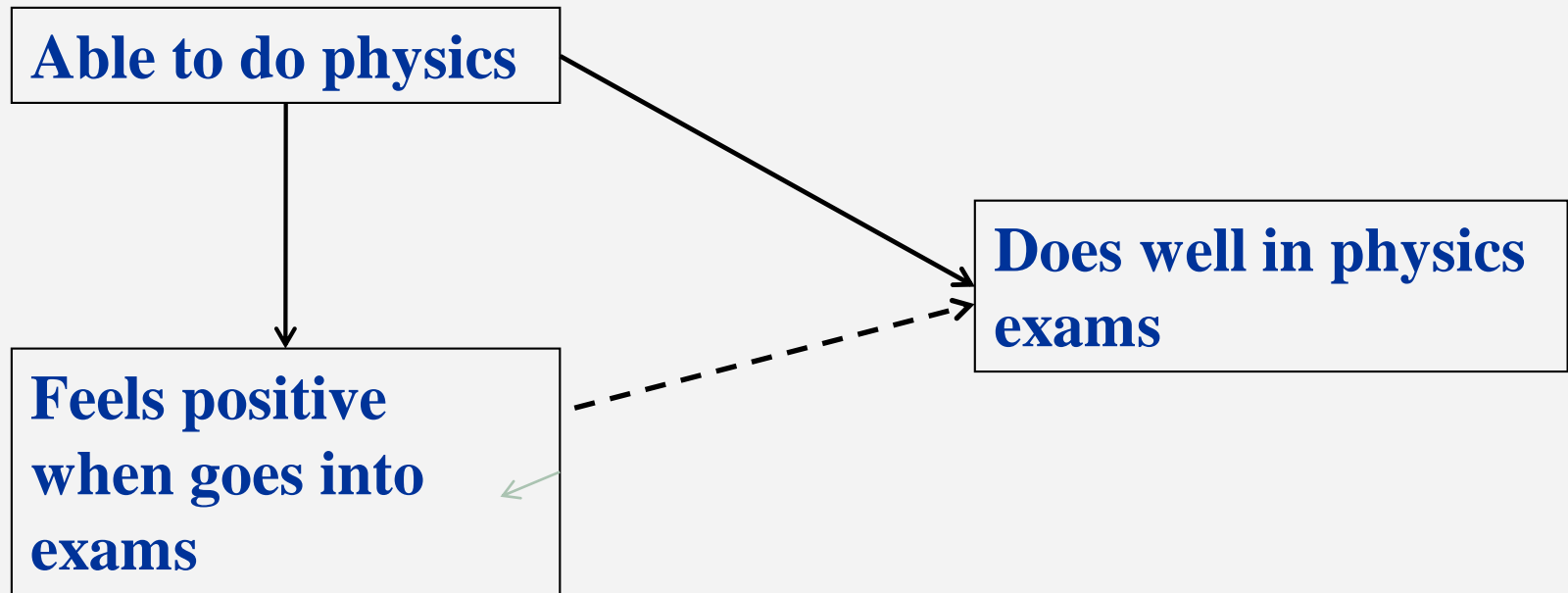
- Confounding
- Issues of common effects



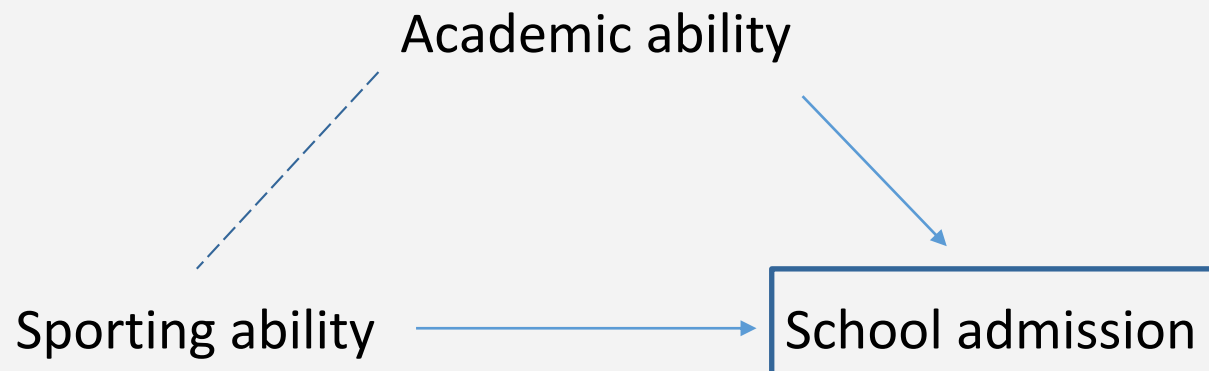
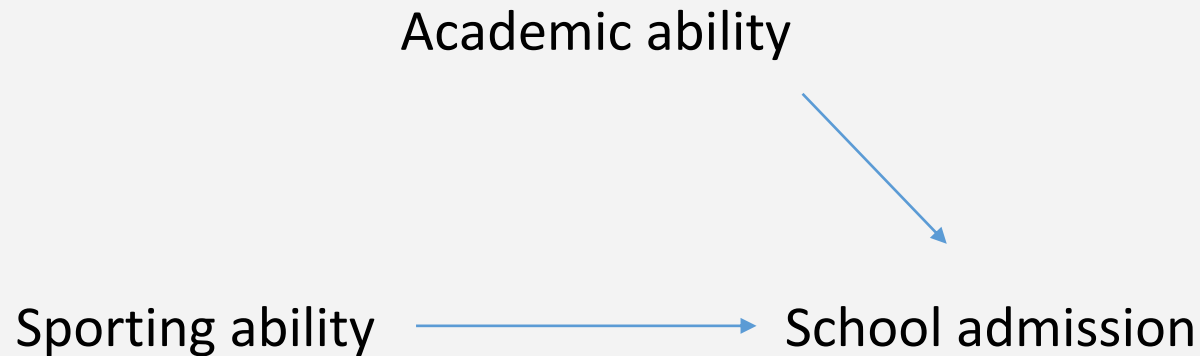
# Confounding

- People who are positive when they go into exams get one grade higher
- Therefore make sure people feel positive to improve grades
- “Maybe they are positive because they know the work”

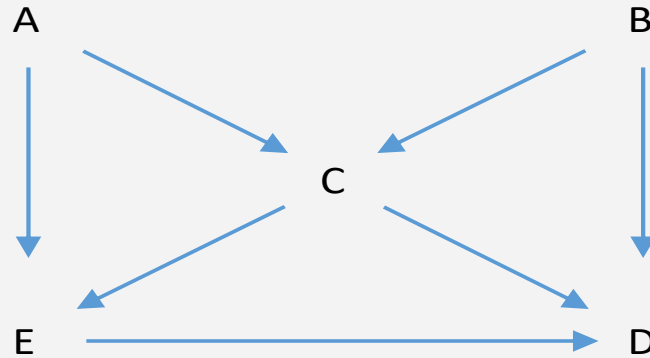




# Caution.....common effects

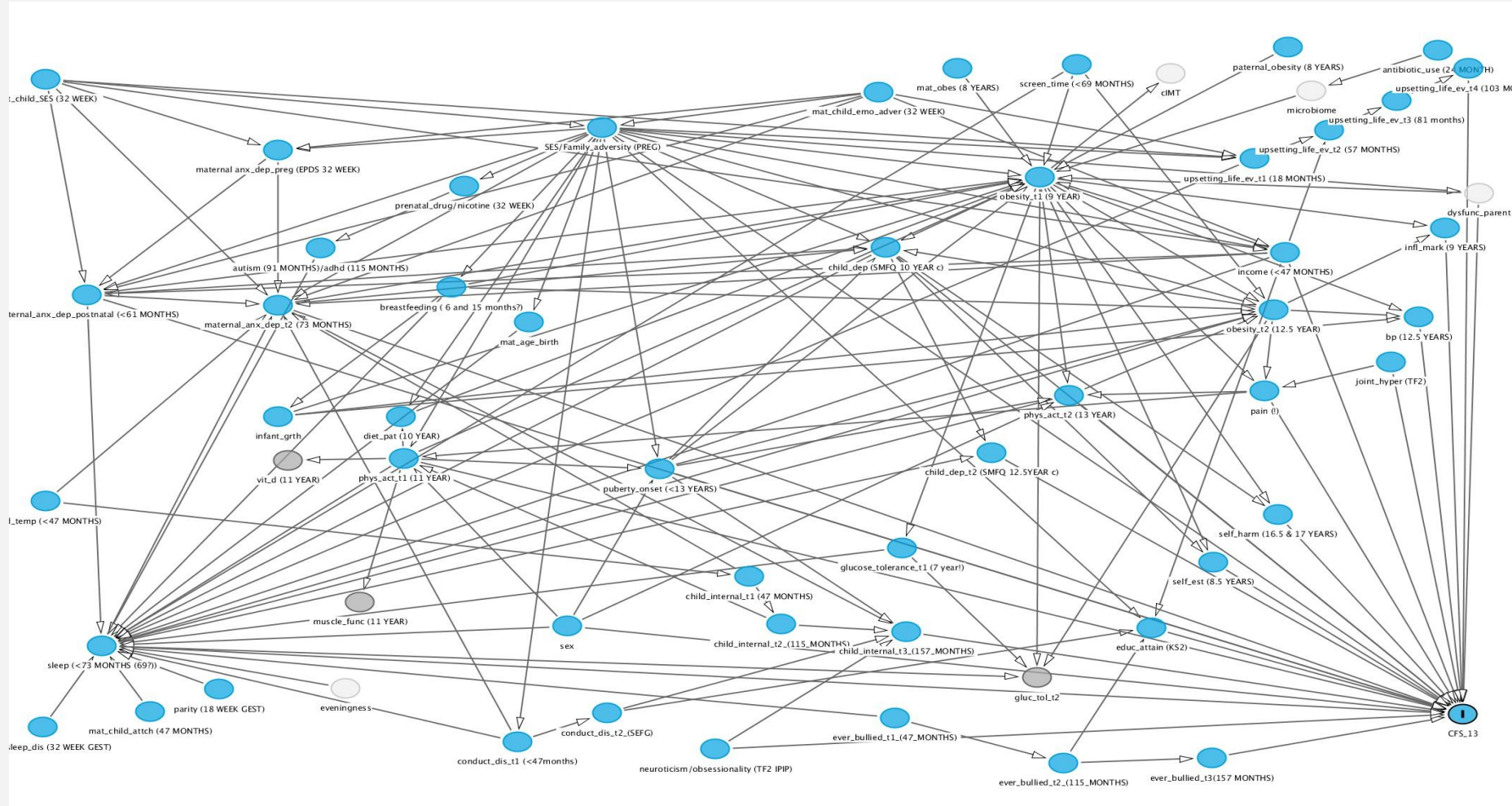


# Directed Acyclic Graphs (DAGs)

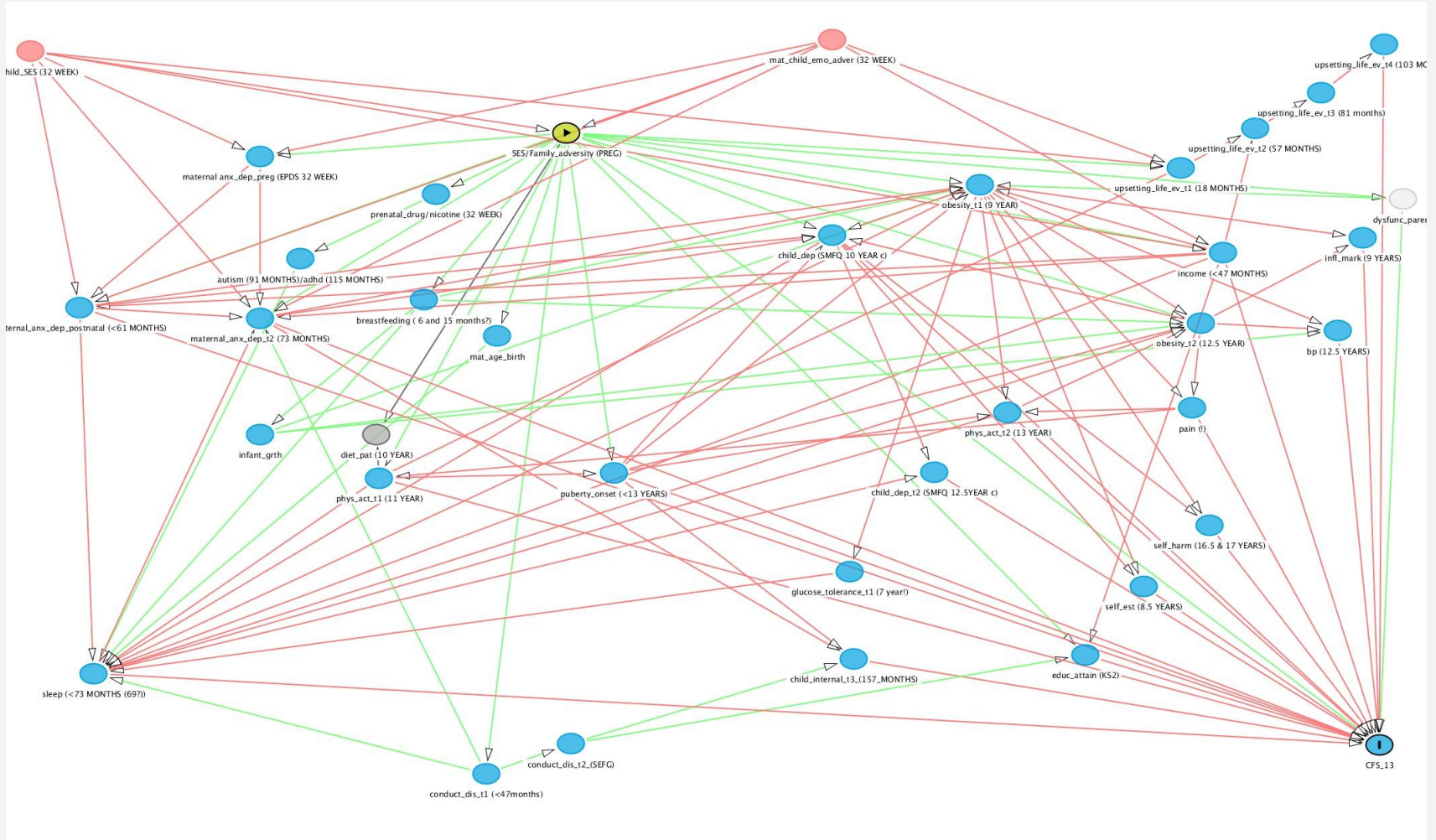


**What should we condition on/ adjust for to address confounding?**

# Relationship between variables



# An example: Family Adversity Index





# Then we

- Used complete case analyses
- Crude analyses
- If an association observed, adjusted for sex and Family Adversity Index
- Multiple Imputation



# Possible common causes

- SES and family adversity
  - Child abuse/trauma
- Childhood anxiety and depression
  - Maternal risk factors
    - Physical activity
      - BMI
    - Blood pressure
      - Sleep
      - Puberty

Meeting with clinical experts.....

# New variables

	CFS 13 years	CFS 18 years
BMI	No	No
BP	Diastolic (v weak)	No
Physical Activity	Yes	No
Sleep	Yes	Yes
Life events	No	Yes
Puberty	No	No

# Sleep

Sleep Medicine 46 (2018) 26–36



Contents lists available at ScienceDirect

## Sleep Medicine

journal homepage: [www.elsevier.com/locate/sleep](http://www.elsevier.com/locate/sleep)



### Original Article

## Childhood sleep and adolescent chronic fatigue syndrome (CFS/ME): evidence of associations in a UK birth cohort



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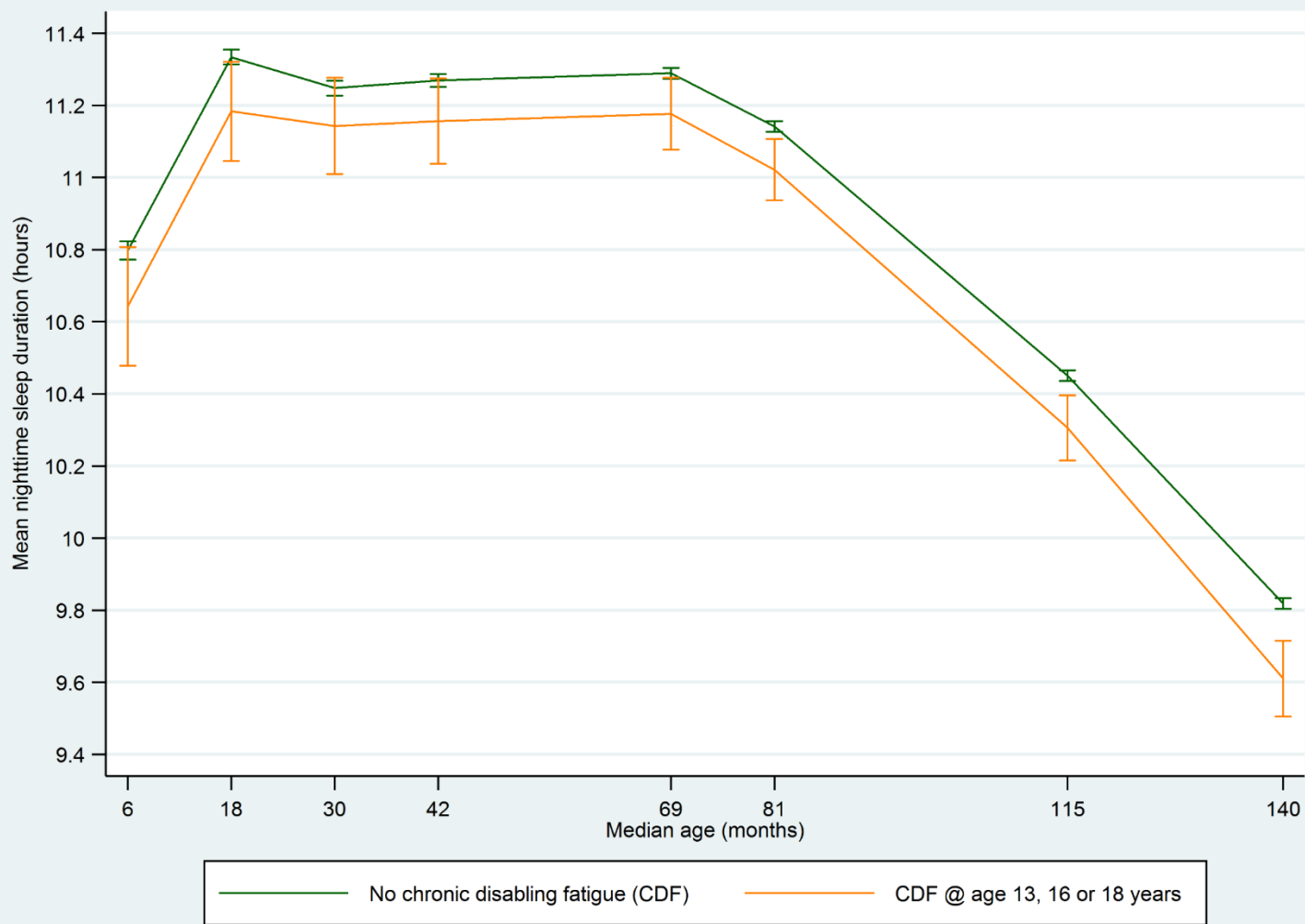
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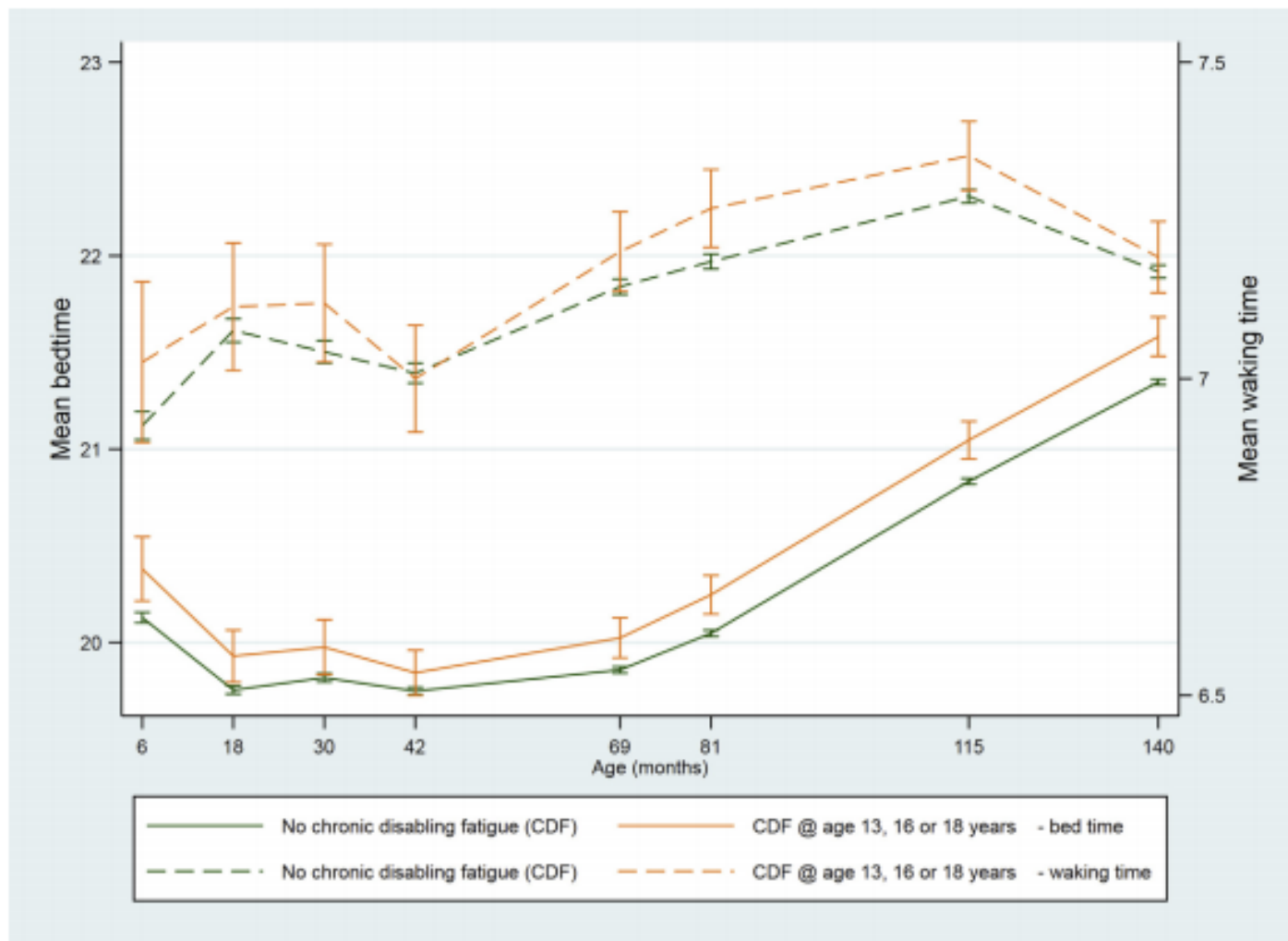
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### ARTICLE INFO

### ABSTRACT





**Fig. 7.** Mean bedtime and waking time at age 6–140 months among children who did or did not develop chronic disabling fatigue (CDF) at age 13, 16 or 18 years (vertical bars indicate 95% CI).



# Physical activity at age 11 years and chronic disabling fatigue at ages 13 and 16 years in a UK birth cohort

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2017-314138>).

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## ABSTRACT

**Objective** To investigate associations of physical activity at age 11 years with chronic disabling fatigue (CDF) at ages 13 and 16 years.

**Design** Longitudinal birth cohort.

**Setting** South-West England.

**Participants** Adolescents enrolled in the Avon Longitudinal Study of Parents and Children.

**Outcomes and exposures** We identified adolescents who had disabling fatigue of >6 months' duration without a known cause at ages 13 and 16 years. Total and moderate-to-vigorous physical activity and sedentary time at age 11 years were measured by accelerometry over a 7-day period.

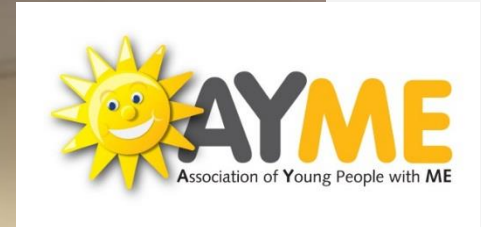
**Results** A total physical activity level 100 counts/min higher at age 11 years was associated with 25% lower odds of CDF at age 13 years (OR=0.75 (95% CI 0.59 to 0.95)), a 1% increase in the proportion of monitored time spent in moderate-to-vigorous activity was associated with 16% lower odds of CDF (OR=0.84 (95% CI 0.69 to 1.01)) and a 1-hour increase in sedentary time was associated with 35% higher odds of CDF.

## What is already known on this topic?

- Lower levels of childhood physical activity were reported to be associated with increased risk of chronic fatigue syndrome (also known as ME) during adulthood.
- It is unclear whether physical activity is a risk factor for the development of chronic fatigue during adolescence.

## What this study adds?

- Children who were less physically active and more sedentary at age 11 years had an increased risk of chronic disabling fatigue at 13 years.
- These associations were not evident at age 16 years, and could be explained by reverse causation.







# EXTRA SLIDES

# MAGENTA: Activity Management

- Er, yeah, because like, at the start of the trial I was like, really ill, but now that I've reduced a lot of stuff, I still am ill but I ... like, I'm not as ill physically as I would be [if I didn't do AM]
- [AM] gives you a bit more flexibility of like "oh yeah I can go out for 4 hours with my friends or I can do four hours of watching movies that I have watched before and stuff like that". I like that flexibility of even though you are sticking to something, you are sticking to something that you can do a lot with.
- MUM: Oh I think it's [AM] great, yeah. I think it's a good- I mean it is a way forward, it is how we find out, you know, what is the way to improve....definitely useful.

# MAGENTA: GET

- I was expecting it to be really like scary. They wouldn't understand what I was talking about and what I had...it's like they understand, like what you have... you can pace yourself with it and you don't have to do it all in one go....it helped me like ... push through ...and get there...getting back with my friends. Erm because I had been away and off school for so long because I was really ill, erm when I got back I couldn't find anyone who wanted to be my friend....Erm I have got my friends back

# GET

- they've been very flexible because I'm trying to play a little bit of netball each week, and with other things I think it's been helpful, and, what was I saying? [laugh], I think with the daily walks, I wasn't quite expecting that, but I think that's been really good for me, I think that's, that's been really good, it's stopped me being quite as lethargic, getting out every day, definitely, and yeah, my fitness has improved, which has made just normal walking around quite a bit easier I think, and less tiresome, so I think that's a real positive, yeah.

# GET

- I suppose if you have CFS you'll be a bit more insecure because obviously you gain weight but there's nothing you can do about it so that's why lots of people like the graded exercise one because then it's gently easing yourself back into it..
- Mum: it's been really flexible to meet his needs so erm, the... the exercise initially it was increased because [participant] could cope with that at the time and it's decreased with, you know, [participant] needs changed and erm, erm, cos he was coping with other things as well, and so erm, the exercise has decreased to allow for that for the moment and I'm very confident that when we go back [clinician] will listen to everything he says and... and you know, change it accordingly and appropriately really.

# Mum

- I, err, I've definitely noticed an improvement. It's definitely good. The regime, everything...I was worried that um [PARTICIPANT] would overdo it, that he would push himself but he, he hasn't. He stuck to it. He's done everything that everybody's told him and he – I'm sure he will say he feels better. There are days that I can say I've asked him to do things and he says "Mum, I, I really don't feel I can do that".