# PROFILING THE INFLAMMATORY STATUS OF ADIPOSE TISSUE AND EVALUATING ACTIONS OF OMEGA-3 FATTY ACIDS IN HUMAN OBESITY
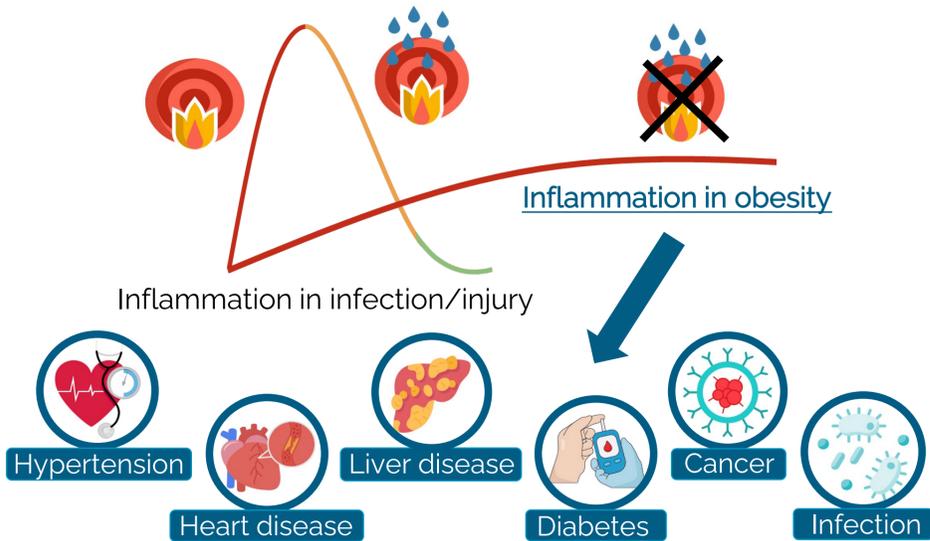
Fisk HL[1], Ayres R[1], Antoun E[1], Childs CE[1], Kuda O[2], Kopecky J[3], Lillycrop KA[1] and Calder PC[1].
[1] Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, [2] Department of Adipose Tissue Biology, Institute of Physiology of the Czech Academy of Sciences, Prague, Czech Republic. [3] Institute for Clinical and Experimental Medicine, Prague, Czech Republic

**University of Southampton**

## Why are we interested in inflammation in adipose (fat) tissue in obesity?



Inflammation in infection/injury

Inflammation in obesity

Hypertension · Heart disease · Liver disease · Diabetes · Cancer · Infection

- 64% of the UK adult population are living with overweight and obesity.
- Obesity related illness costs the NHS £6.1bn a year and the wider economy £27bn a year.
- A poorly understood cause of obesity related diseases is <u>inflammation</u> which stems from the adipose (fat) tissue when there is increased fat storage.
- Adipose tissue has important roles in controlling energy storage and release, blood sugar, and regulating our immune system. This malfunctions in obesity.
- We may be able to improve health and prevent /reduce inflammation through nutrition such as using omega-3 fats (fatty acids).
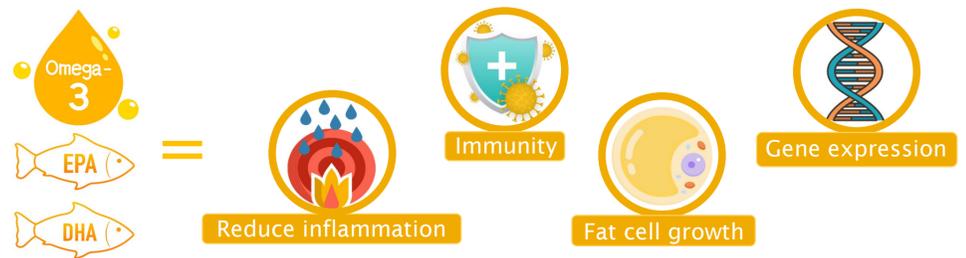
### What do we want to know and why?

- **How** does inflammation occur in the adipose tissue in obesity?
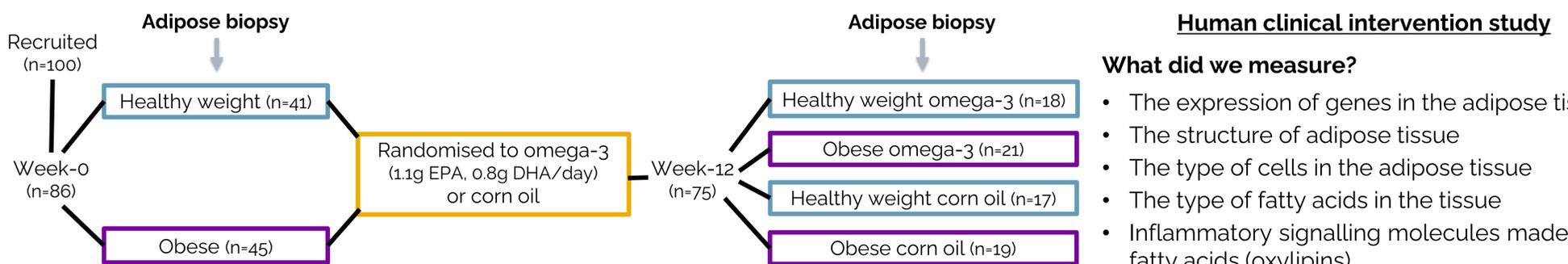- **Can**, and **how** do omega-3 fats regulate inflammation in adipose tissue?

## Why are we interested in omega-3 fatty acids?

The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) occur naturally in fatty fish and fish oil. They have been shown to reduce inflammation and affect the expression of genes involved in lipid metabolism, cell growth, and inflammatory and immune responses.

Therefore, they may be a promising solution to limiting adipose tissue inflammation in obesity, but this has not been reported before.

Omega-3  EPA  DHA = Reduce inflammation · Immunity · Fat cell growth · Gene expression

## What did we investigate and how?

Recruited (n=100)

Week-0 (n=86)

Adipose biopsy

Healthy weight (n=41)

Obese (n=45)

Randomised to omega-3 (1.1g EPA, 0.8g DHA/day) or corn oil

Week-12 (n=75)

Adipose biopsy

Healthy weight omega-3 (n=18)
Obese omega-3 (n=21)
Healthy weight corn oil (n=17)
Obese corn oil (n=19)
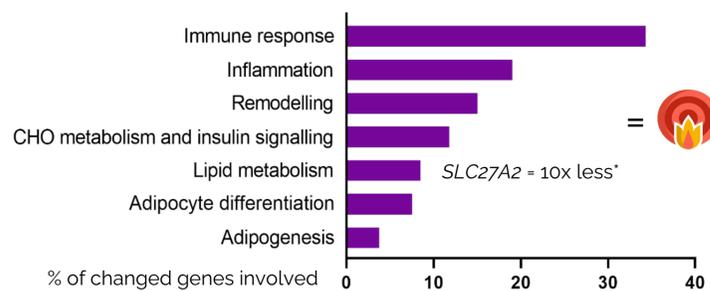
### Human clinical intervention study
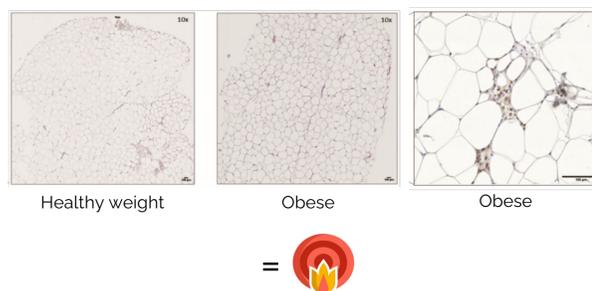
**What did we measure?**
- The expression of genes in the adipose tissue
- The structure of adipose tissue
- The type of cells in the adipose tissue
- The type of fatty acids in the tissue
- Inflammatory signalling molecules made from fatty acids (oxylipins)

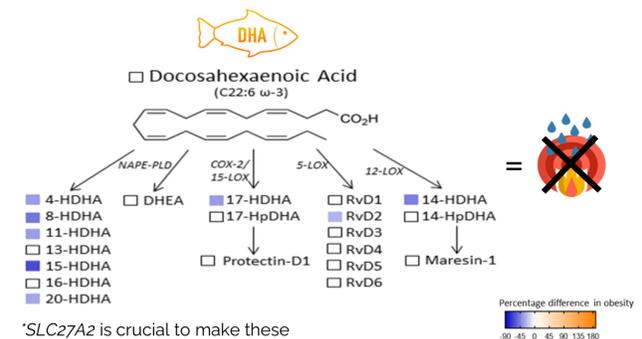## What did we find - How did inflammation occur in adipose tissue in obesity?

**1. Changes to expression of genes associated with:**



Immune response · Inflammation · Remodelling · CHO metabolism and insulin signalling · Lipid metabolism · Adipocyte differentiation · Adipogenesis

% of changed genes involved   0  10  20  30  40

*SLC27A2* = 10x less*

**2. Enlarged fat cells and immune cells collecting in the tissue**



Healthy weight · Obese · Obese

**3. Reduced inflammation resolving oxylipins**



DHA

□ Docosahexaenoic Acid (C22:6 ω-3)

NAPE-PLD · COX-2/15-LOX · 5-LOX · 12-LOX

4-HDHA, 8-HDHA, 11-HDHA, 13-HDHA, 15-HDHA, 16-HDHA, 20-HDHA · DHEA · 17-HDHA, 17-HpDHA · RvD1, RvD2, RvD3, RvD4, RvD5, RvD6 · 14-HDHA, 14-HpDHA · Protectin-D1 · Maresin-1

*SLC27A2* is crucial to make these

Percentage difference in obesity   -90 -45 0 45 90 135 180

## What did we find - Could omega-3 reduce inflammation?

**Omega-3 Supplementation resulted in:**

- An increase in adipose tissue levels of EPA and DHA – figure 1.
- A decrease in pro-inflammatory oxylipins from arachidonic acid – figure 2.
- An increase anti-inflammatory oxylipins from EPA and DHA but **not in obesity** – figure 3.
- Decreased expression of genes involved in inflammation and immune response, but **less of a response in obesity** – figure 3.

## What does this mean and why is it important?

- Reduced levels of anti-inflammatory oxylipins are a key feature of obesity.
- Omega-3 fatty acids can increase anti-inflammatory oxylipins but not in obesity. This may be due to lower expression of *SLC27A2*.
- Individuals living with obesity do not get the same health benefits that healthy weight individuals do, yet recommended intakes of omega-3 are not given for obesity (SACN dietary reference values – GOV.UK). This requires revision.
- I have identified a gene (*SLC27A2*) that may contribute to inflammation and poor response in obesity which could be targeted to improve health in this group.



People of a healthy weight

People living with obesity

*SLC27A2* = 10x less

**1.**



% EPA · % DHA

Healthy weight week-0 · Healthy weight week-12 · Obese week-0 · Obese week-12

*$P \leq 0.050$
**$P \leq 0.001$

**2.**



$P$   1.0  0.8  0.6  0.4  0.2  0.0

Healthy weight – Omega-3 · Obese – Omega-3 · Healthy weight – Corn oil · Obese – Corn oil

Arachidonic Acid · EPA · DHA

+ Increase  − Decrease

**3.**



Log FC   2  0  -2

Healthy weight – Omega-3 · Obese – Omega-3 · Healthy weight – Corn oil · Obese – Corn oil

Fold change
More expressed
Less expressed