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Longevity and Biological Ageing: Enhancing Health into Advanced Age



SESSION 4

Professor Anna Nicolaou

Skin Barrier Bioactive Lipids, The Gut–Skin Axis, Hormonal Influence, and Healthy Skin Ageing

2:00-2:45pm

An event by:  Nutritional Medicine Institute

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# Skin Barrier Lipids: Linking Hormonal Changes, Host-Microbiota Interactions, and Healthy Skin Ageing

**Professor Anna Nicolaou**  
Faculty of Biology Medicine and Health  
The University of Manchester, UK



**NMI SUMMIT 2026**  
Longevity and Biological Ageing:  
Enhancing Health into Advanced Age  
9-10 October, Millennium Gloucester Hotel, London

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## Affiliations and Declarations of Interest

### Affiliations

- Professor of Biological Chemistry, School of Health Sciences and Lydia Becker Institute of Immunology of Inflammation, Faculty of Biology Medicine and Health, The University of Manchester

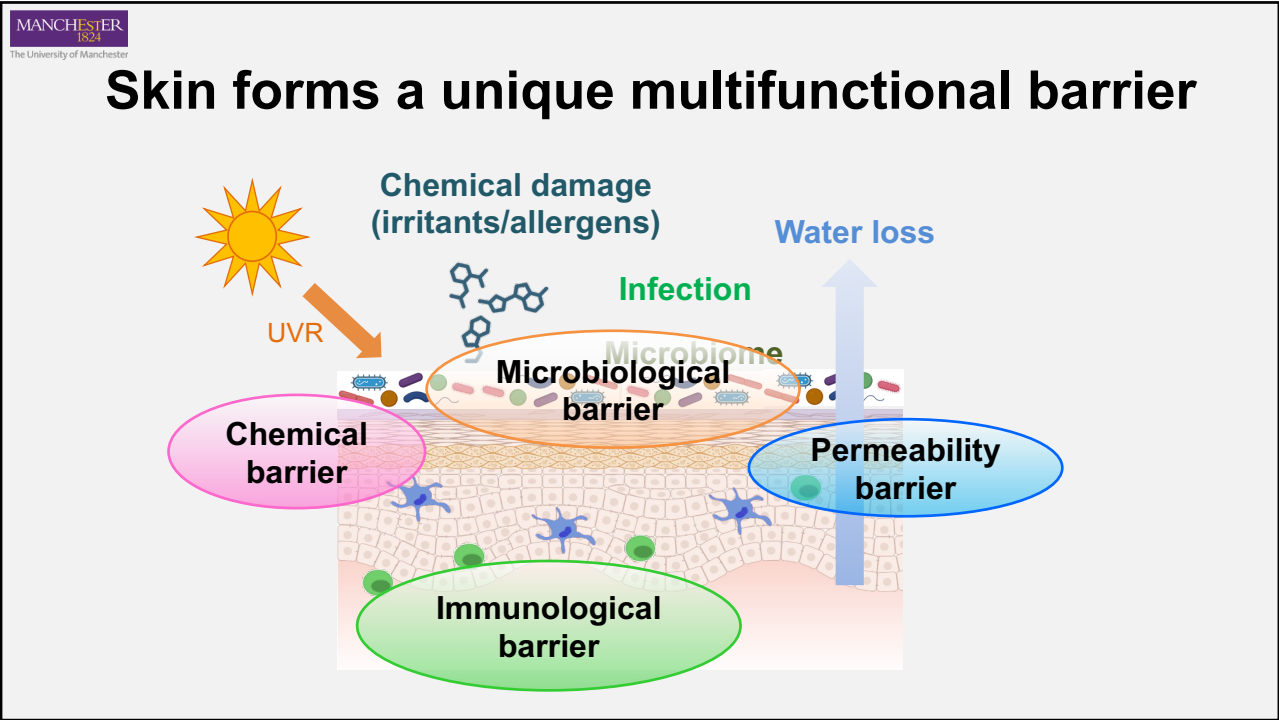
### Boards and Editorships

- President-Elect and Executive Board Member: International Society for the Study of Fatty Acids and Lipids (ISSFAL)
- Editorial Boards (Elsevier): BBA Lipids, Progress in Lipid Research

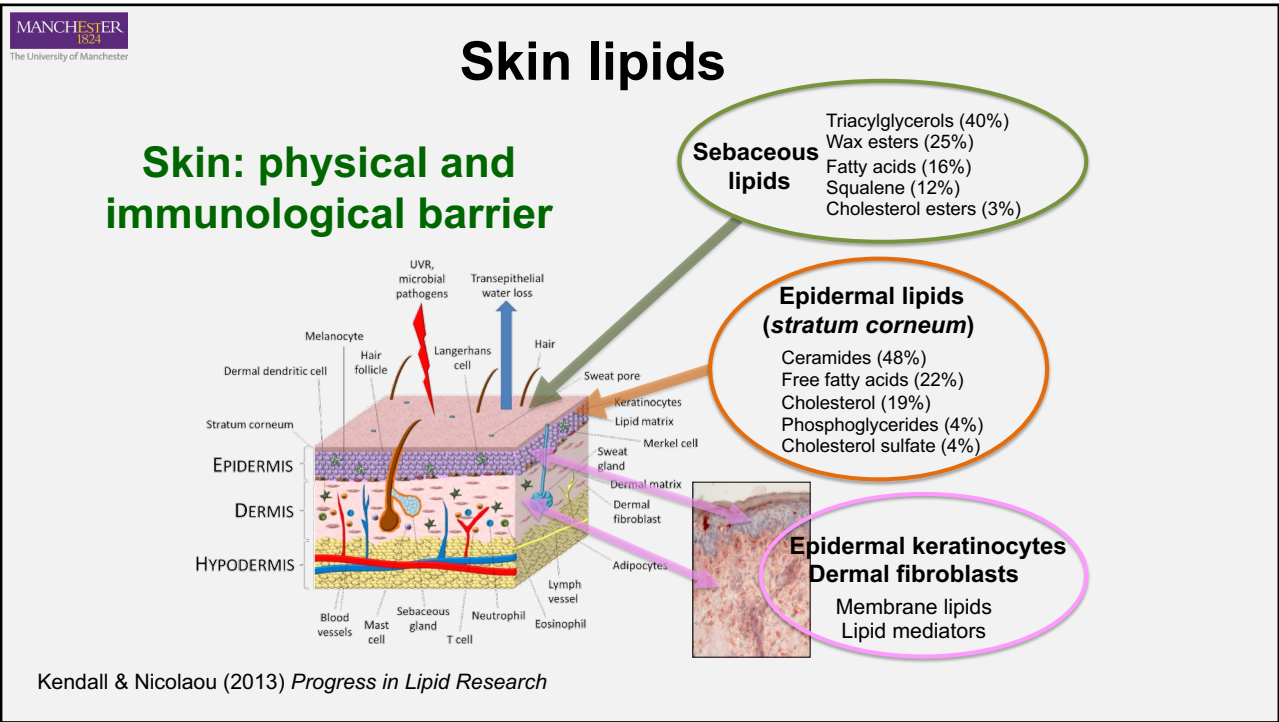
### Industry Research Funding and Consultancies

- Boots plc, Unilever, AstraZeneca, Waters, UoMIF, Intercos

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**Lipids are involved in all aspects of the skin barrier**

**The physical barrier**

- Corneocyte
- Lipid matrix
- Corneodesmosome
- Tight junction
- Keratinocyte

**The microbiological barrier**

**Skin microbiota**

- Bacteria
- Fungi
- Viruses

**Acid mantle**

- Sebum, sweat
- pH 4.5-5.5
- Acylglycerols
- Free fatty acids
- Bioactive lipid mediators
- Antimicrobial peptides
- Microbial metabolites

**The immunological barrier**

- Bioactive lipid mediators and cytokines
- Langerhans cell
- T cell
- Keratinocyte
- Immune cell infiltrate from dermis

**Lipid changes during epidermal differentiation**

| Layer | Key lipids                                                            |
|-------|-----------------------------------------------------------------------|
| SC    | Ceramides, cholesterol, free fatty acids                              |
| SG    | Glucosylceramides, sphingomyelins, cholesterol sulfate, acylglycerols |
| SS    | Phospholipids, ceramide production                                    |
| SB    | Phospholipids, triacylglycerols                                       |
| BM    |                                                                       |

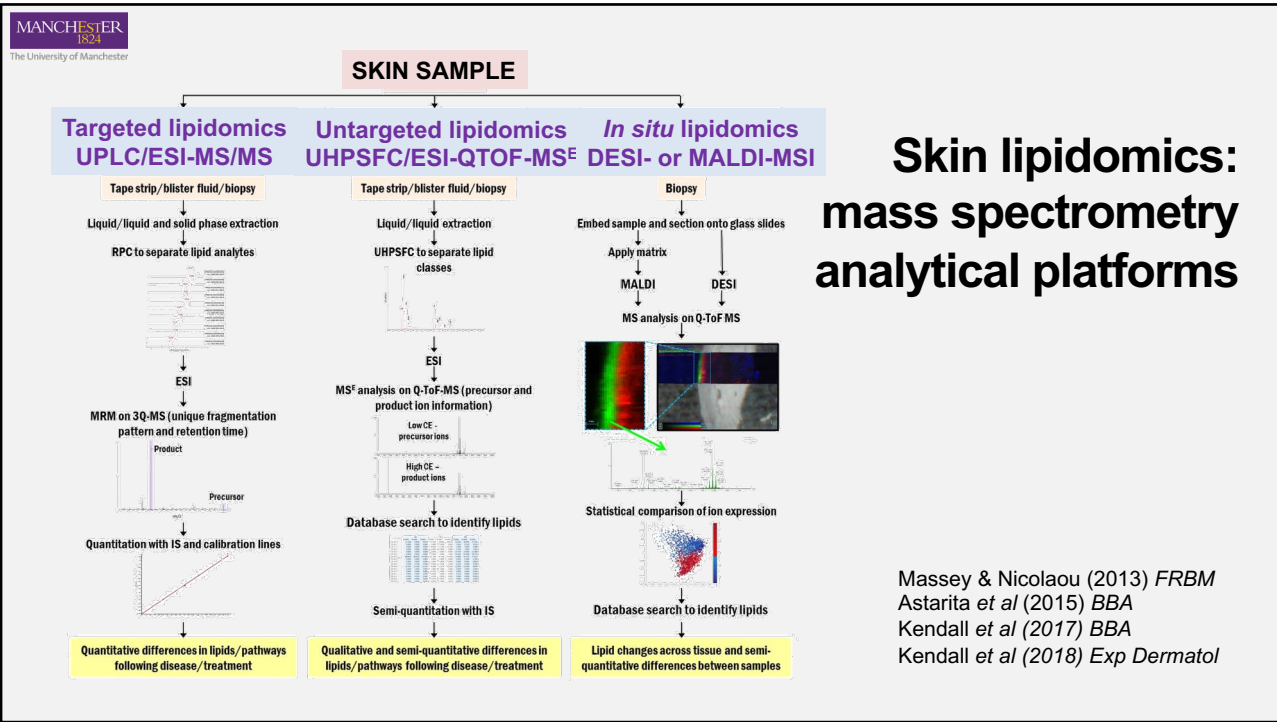
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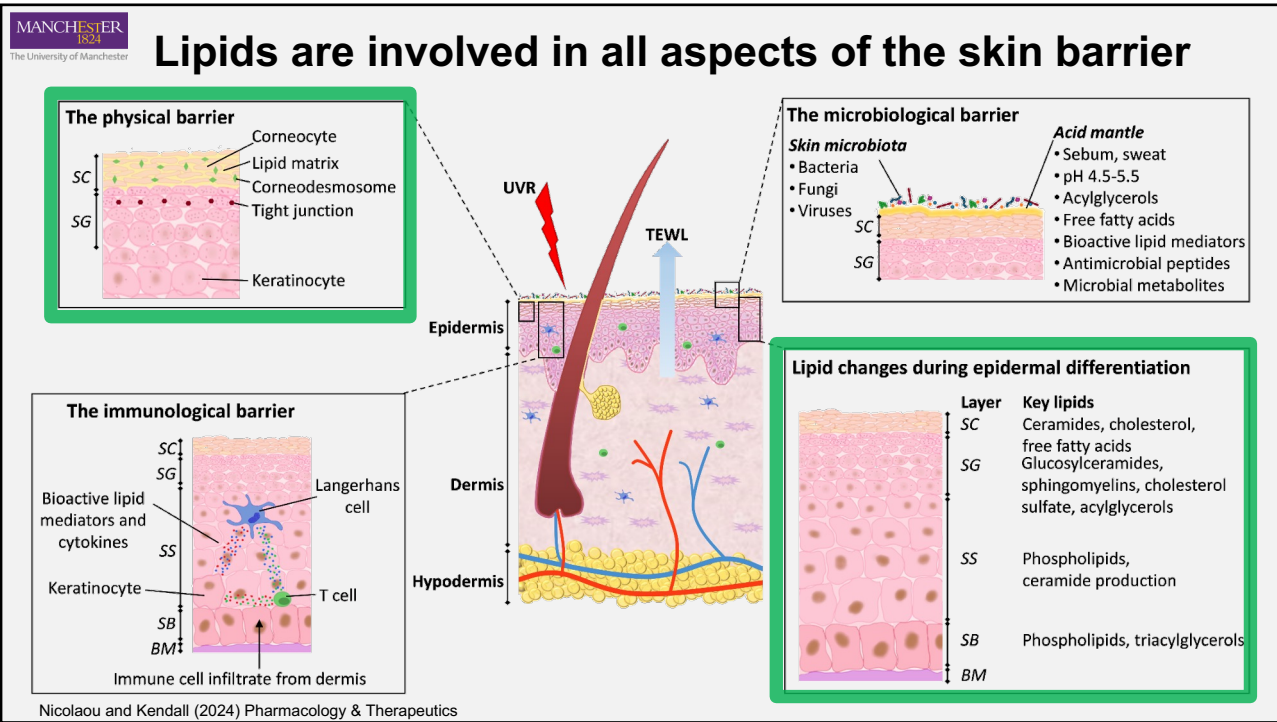
The diagram illustrates various skin sampling methods:

- Tape strips**: A piece of adhesive tape is shown being applied to the skin.
- Stratum corneum**: A close-up of the skin's surface layer.
- Sebum**: A close-up of a skin sample, likely a hair follicle or sebaceous gland.
- Suction blister fluid**: A diagram showing a suction blister being formed on the skin.
- Biopsies**: A diagram showing a skin biopsy procedure, including a cross-section of the skin and a sample being taken.

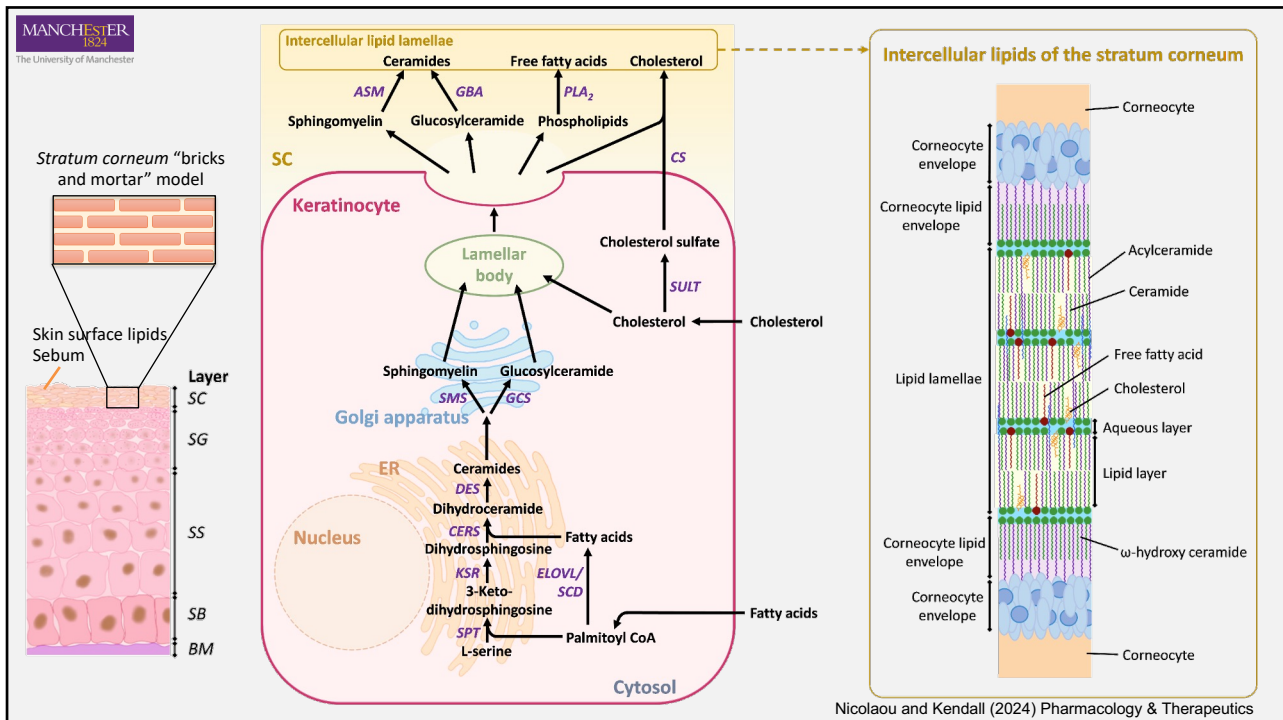
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## Epidermal lipids and barrier dysfunction

Many skin diseases and systemic conditions with cutaneous manifestations demonstrate lipid dysregulation

- Changes in **ceramide** abundance and quality
- Changes in **fatty acid** profiles

Lipid changes associated with:

- Poor barrier function
- Dryness and itching
- Susceptibility to infection
- Diminished ability to repair damage

These symptoms can be present in **aged skin**

The diagram shows a cross-section of the stratum corneum (SC) with the lipid lamellae and corneocyte envelopes. The SC is the outermost layer of the skin, composed of multiple layers of corneocytes (dead skin cells) held together by a lipid-rich matrix. The lipid lamellae are the layers of lipids that form the barrier between the corneocytes. The corneocyte envelopes are the layers of lipids that surround each corneocyte.

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## Skin health declines with age



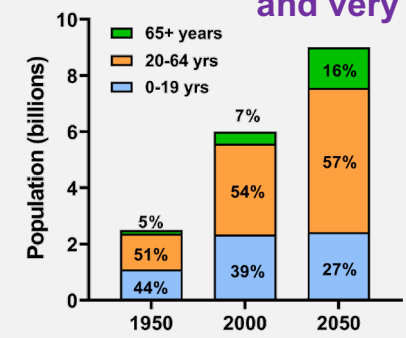
### Ageing leads to visible structural skin changes

- Loss of elasticity; wrinkles
- Exacerbated by photoageing

### Ageing impacts skin barrier function

- Dryness, itching
- Susceptibility to infection
- Diminished ability to repair damage
- Impaired barrier function contributes to systemic “inflammageing”
- Reduced sebum production
- Altered cutaneous microbiota
- Overall health and quality of life

### Worldwide increase in the old and very old



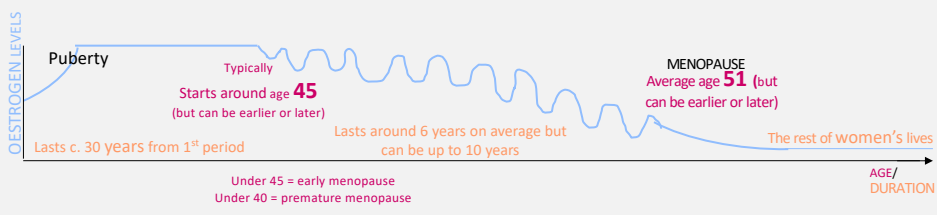
| Year | 0-19 yrs | 20-64 yrs | 65+ years |
|------|----------|-----------|-----------|
| 1950 | 44%      | 51%       | 5%        |
| 2000 | 39%      | 54%       | 7%        |
| 2050 | 27%      | 57%       | 16%       |

UN & WHO reports

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## Impact of skin ageing better studied in women as it is accelerated during the menopause



**OESTROGEN LEVELS**

Puberty

Typically Starts around age **45** (but can be earlier or later)

LASTS c. 30 years from 1<sup>st</sup> period

LASTS around 6 years on average but can be up to 10 years

**MENOPAUSE**  
Average age **51** (but can be earlier or later)

The rest of women's lives

AGE/DURATION

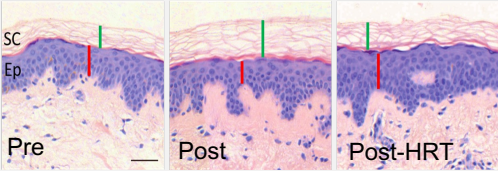
Under 45 = early menopause  
Under 40 = premature menopause

- Menopause occurs as part **chronological ageing** in females
- First clinically significant manifestation of skin ageing
- Declining oestrogen; reduced skin strength and elasticity; increased skin dryness; altered cutaneous immune profile; reduced wound healing capacity

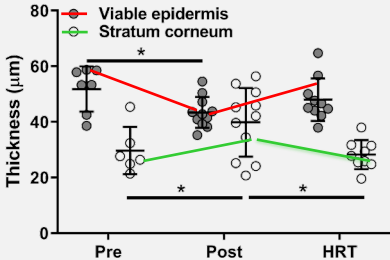
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## Epidermal thickness reduced and *stratum corneum* thickness increased with menopause



Epidermal morphology; H&E staining



| Stage | Viable epidermis (µm) | Stratum corneum (µm) |
|-------|-----------------------|----------------------|
| Pre   | ~58                   | ~25                  |
| Post  | ~45*                  | ~35*                 |
| HRT   | ~52*                  | ~28*                 |

One-way ANOVA with Holm-Sidak's multiple comparisons; \* $p < 0.05$ ;  $n = 7-11$  subjects

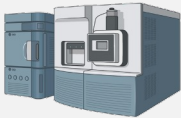
- Hormone replacement therapy (HRT) can alleviate symptoms in some women
- SC thickness partially normalised with HRT indicating regulation of epidermal homeostasis by female hormones – **are ceramides involved?**

Mellody *et al* (2022) JEDV

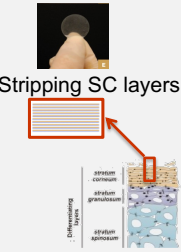
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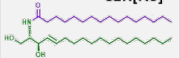
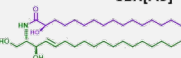
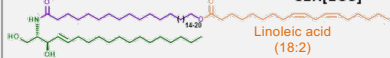
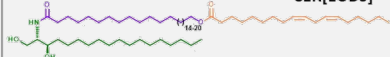
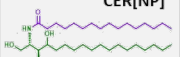
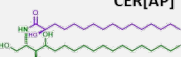
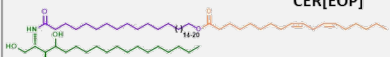
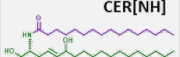
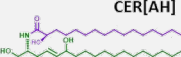
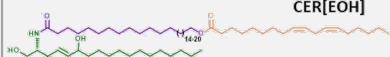
## Ceramide diversity is crucial for the epidermal barrier function



UPLC/ESI-MS/MS  
902 species (12 classes)



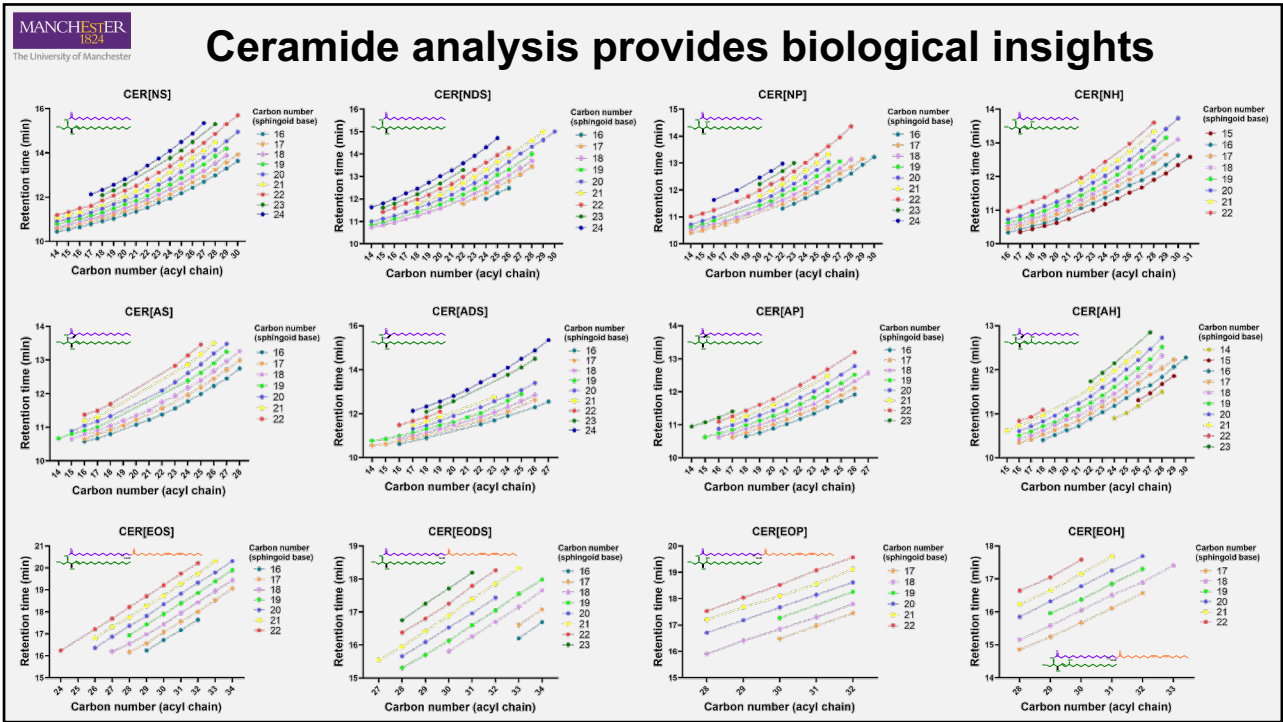
Stripping SC layers

|                | Fatty acid                                                                                                        |                                                                                                                   |                                                                                                                     |
|----------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
|                | Non-hydroxy (N)                                                                                                   | Alpha-hydroxy (A)                                                                                                 | Ester-linked omega-hydroxy (EO)                                                                                     |
| Sphingoid base | <div><div>CER[NS]</div></div>  | <div><div>CER[AS]</div></div>  | <div><div>CER[EOS]</div></div>  |
|                | <div><div>CER[NDS]</div></div> | <div><div>CER[ADS]</div></div> | <div><div>CER[EODS]</div></div> |
|                | <div><div>CER[NP]</div></div>  | <div><div>CER[AP]</div></div>  | <div><div>CER[EOP]</div></div>  |
|                | <div><div>CER[NH]</div></div>  | <div><div>CER[AH]</div></div>  | <div><div>CER[EOH]</div></div>  |

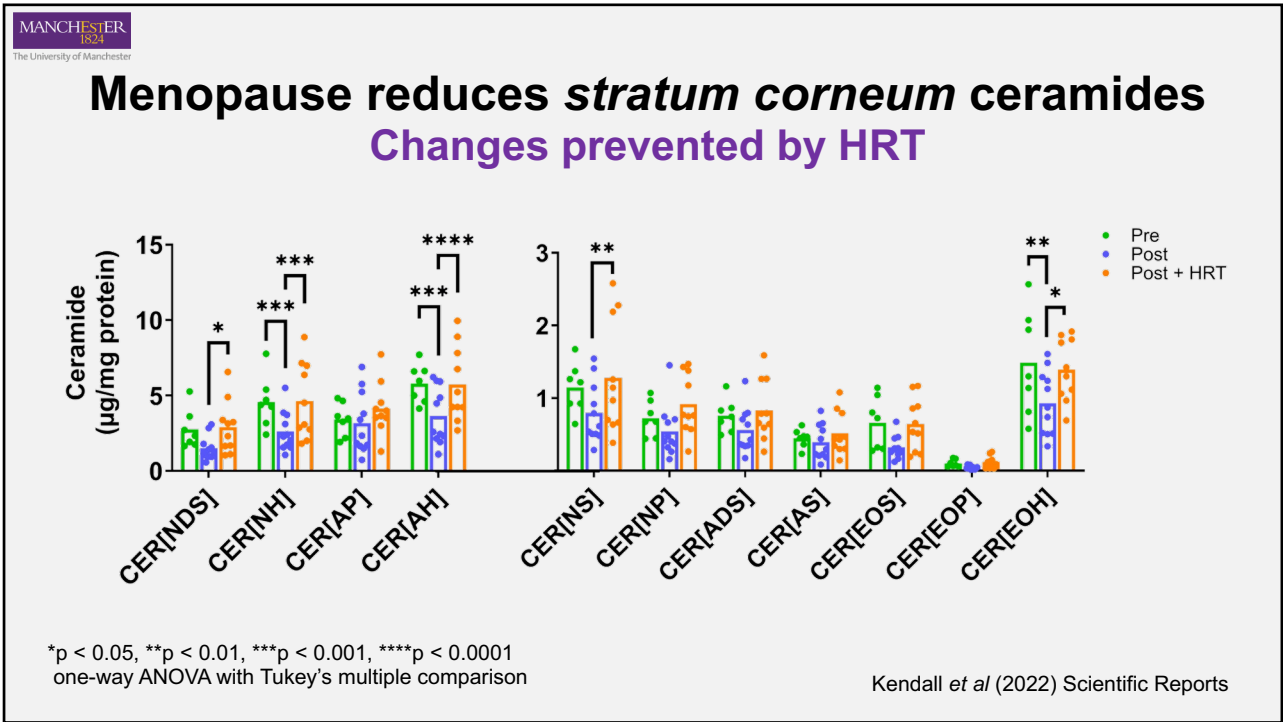
**Human *stratum corneum*:** >1200 ceramides; 21 classes known to date including free and protein-bound species; acyl chains: 52-56C; sphingoid bases: 16-28C

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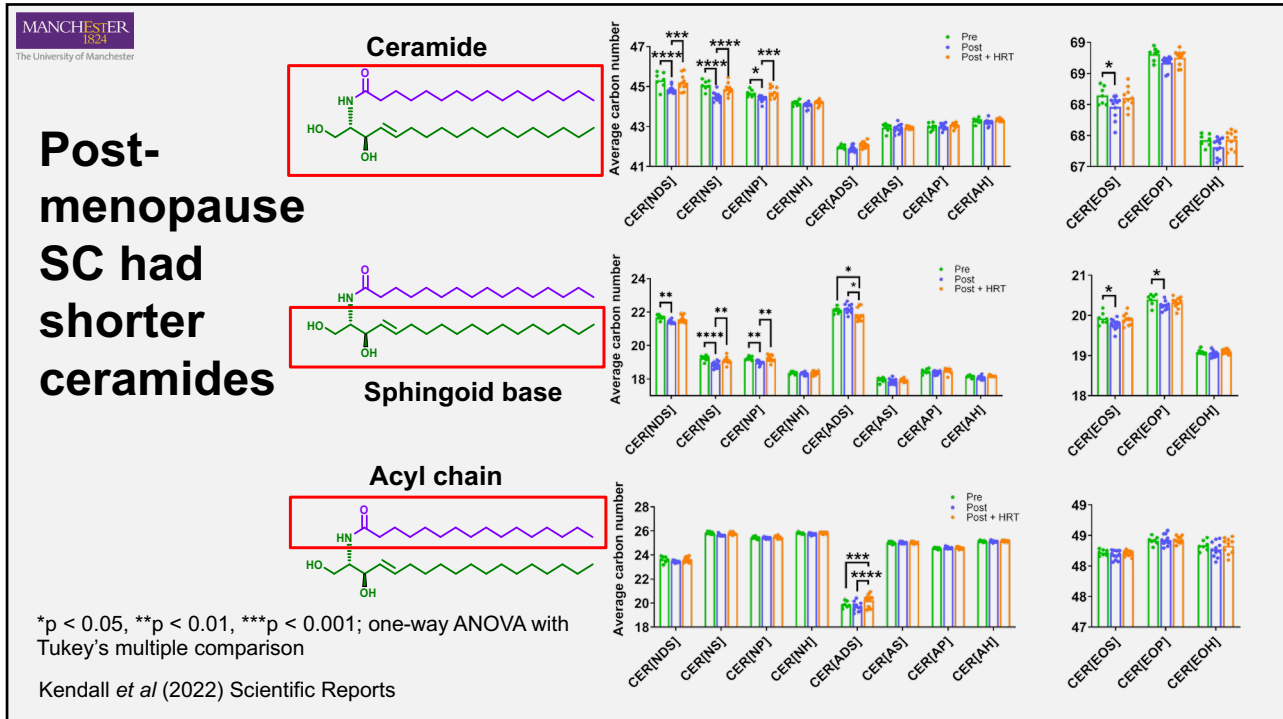
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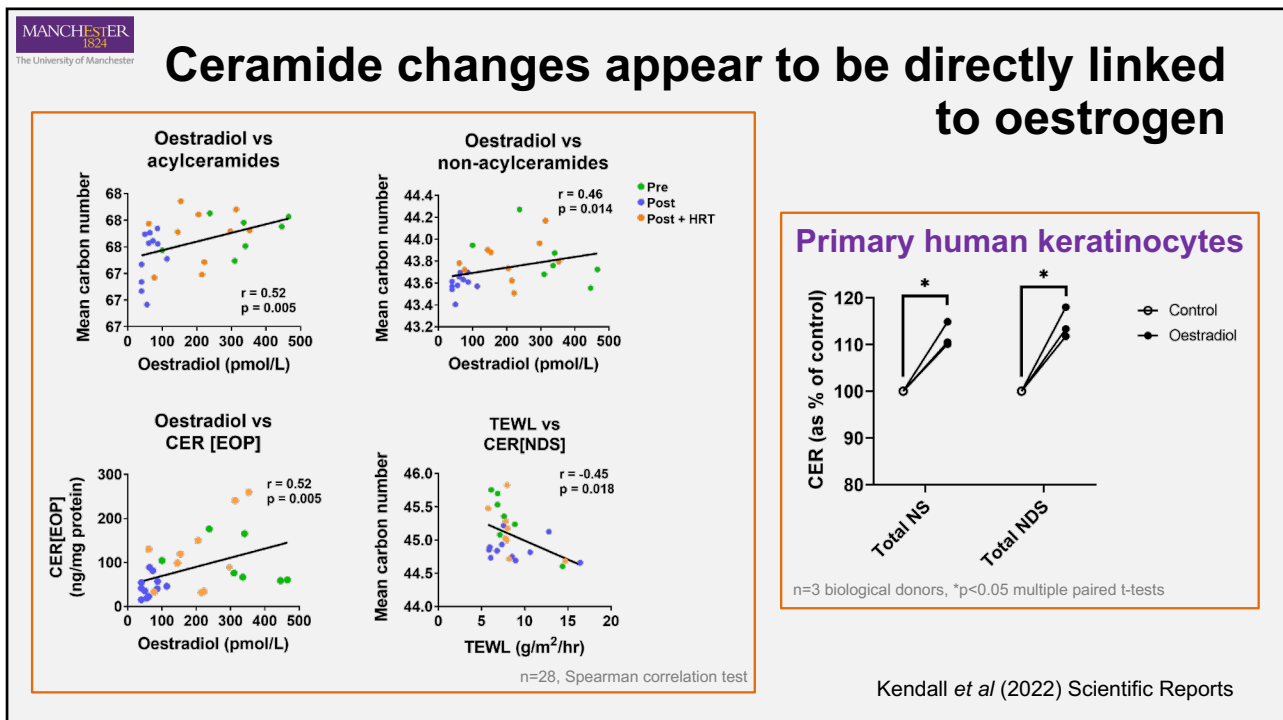
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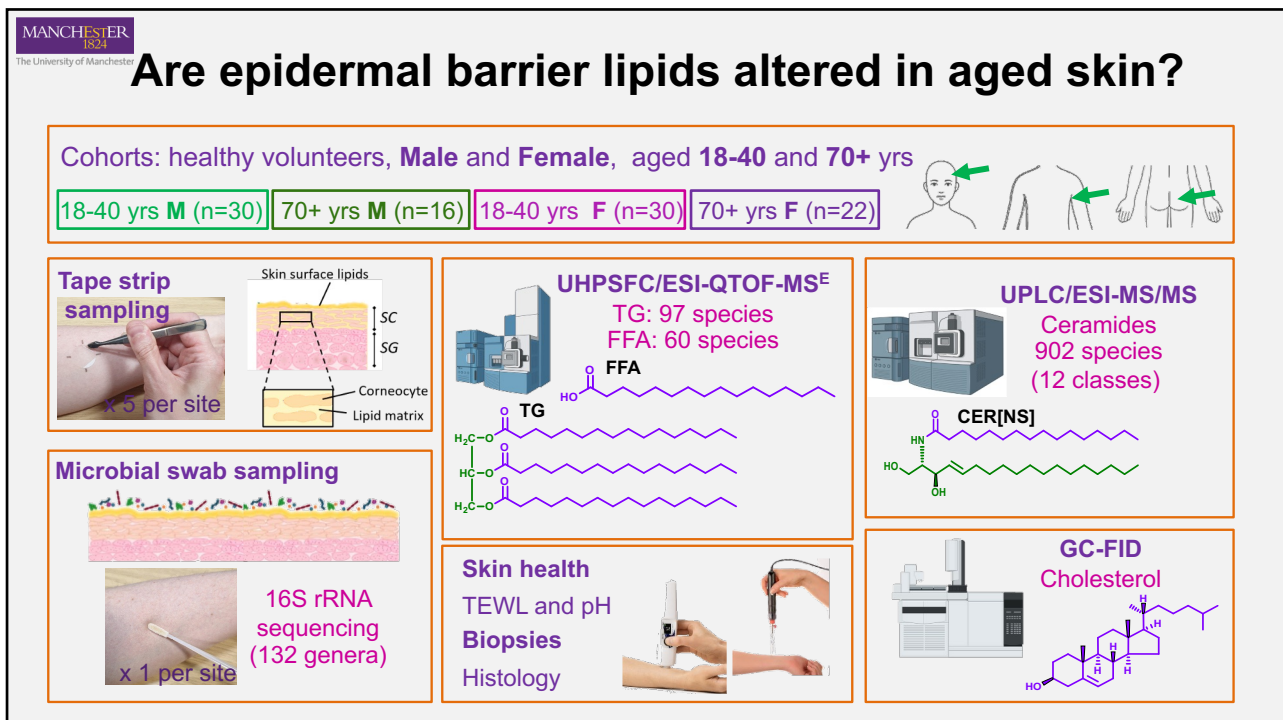
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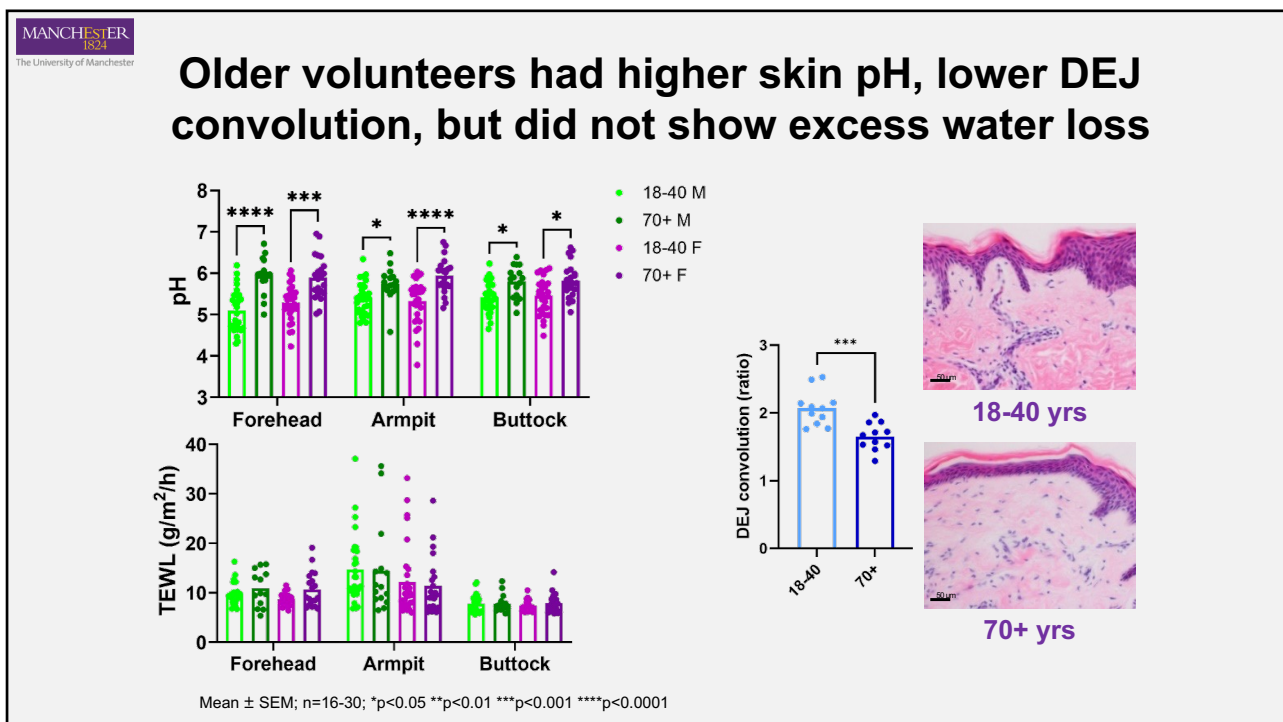
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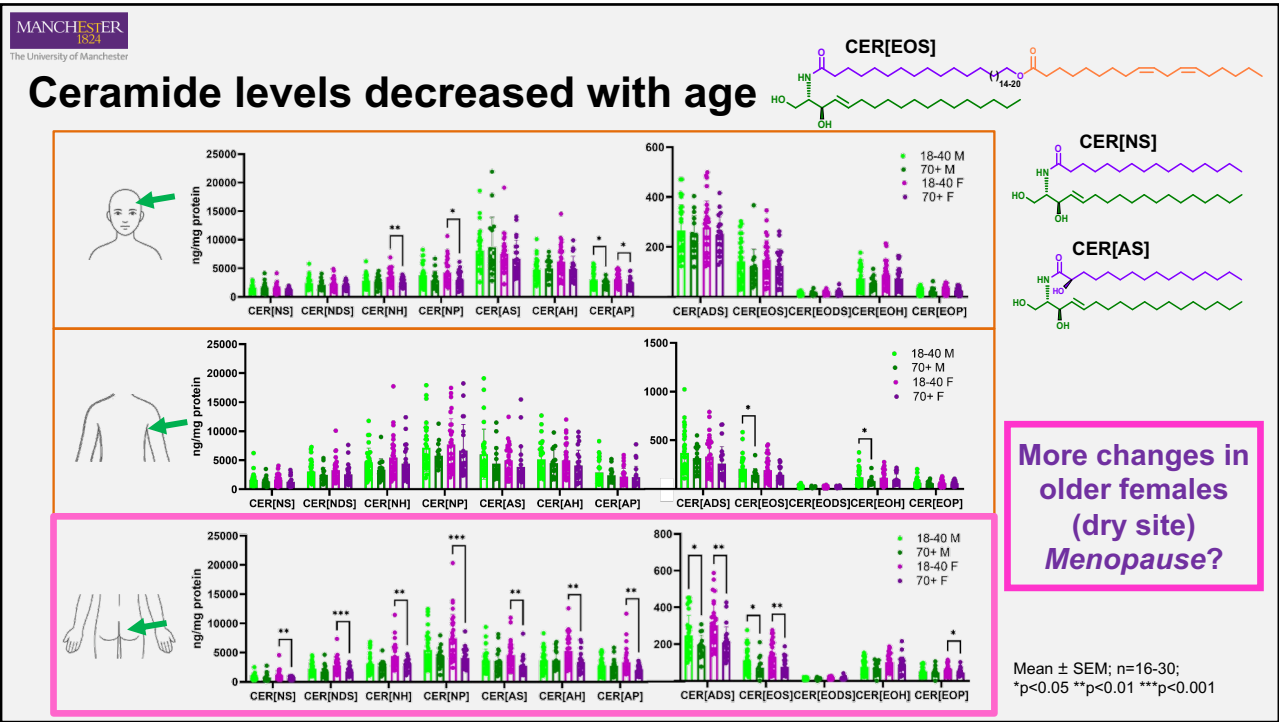
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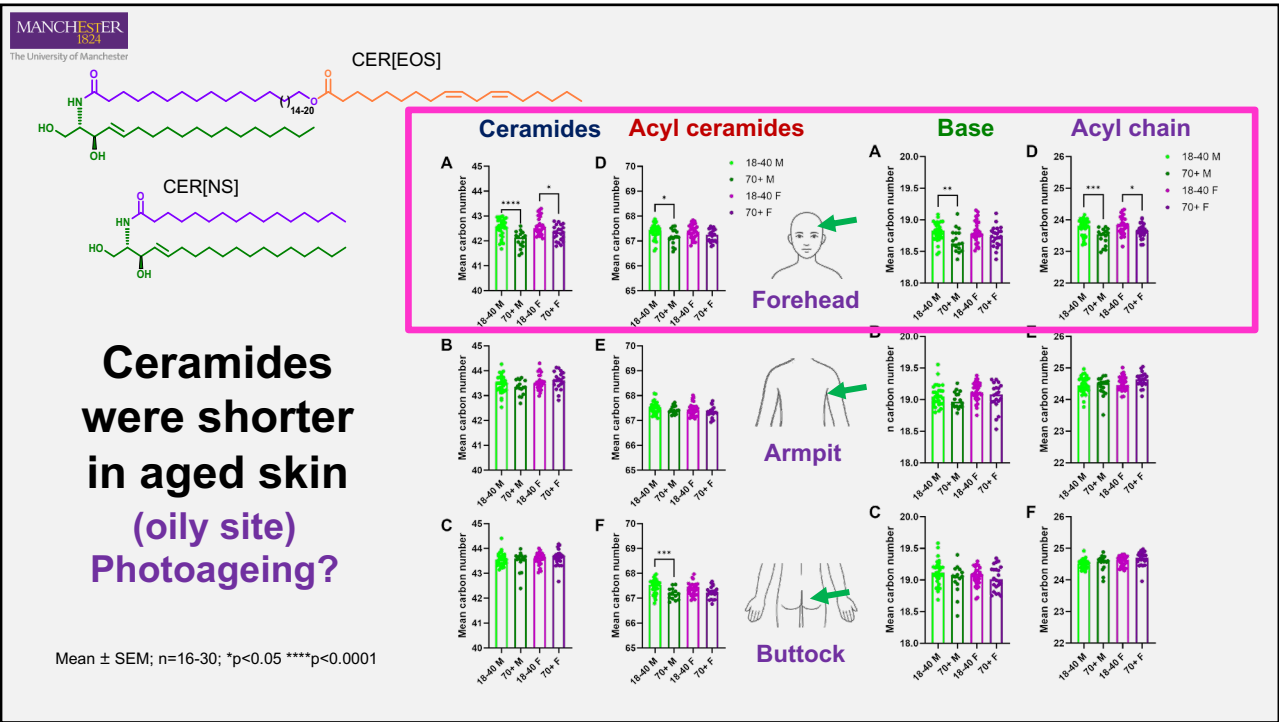
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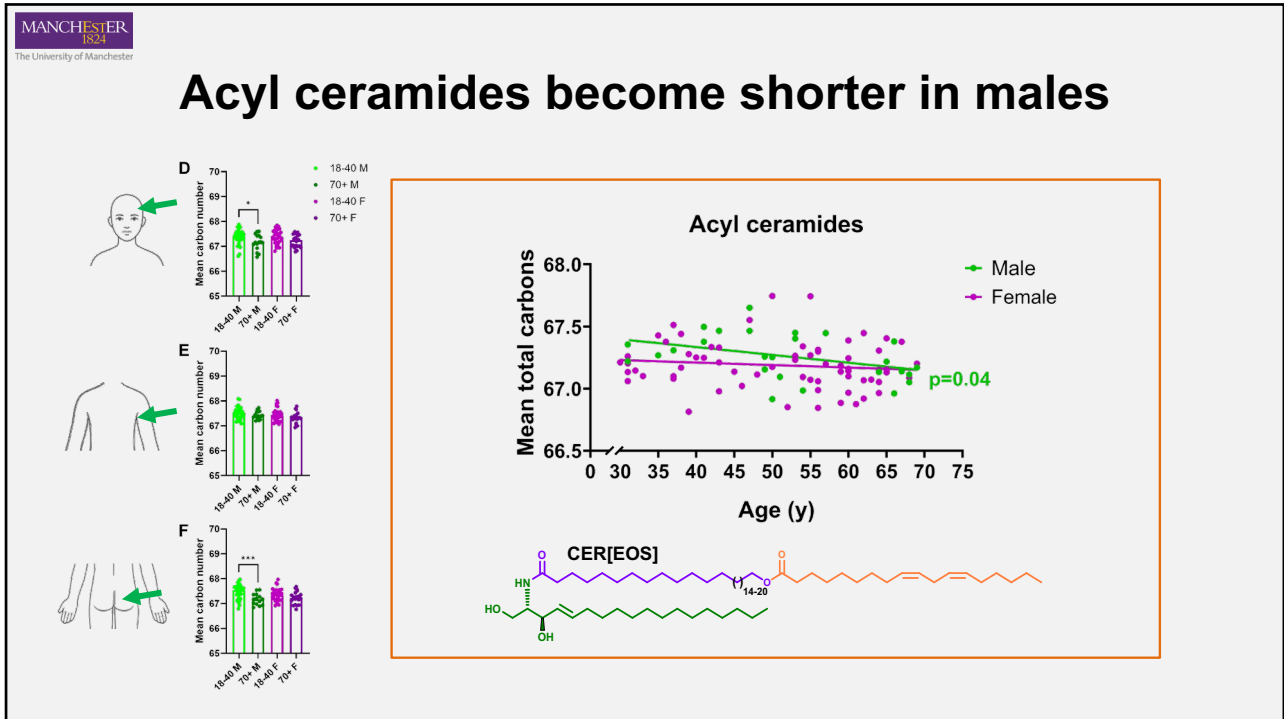
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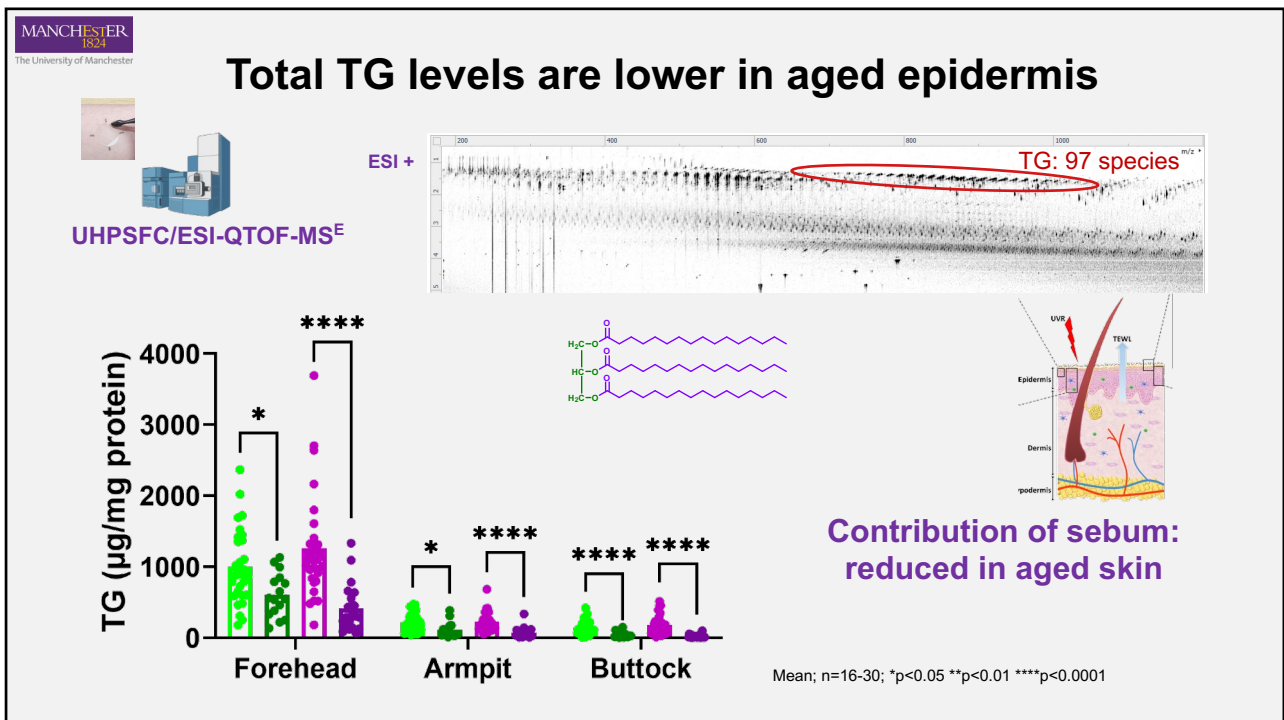
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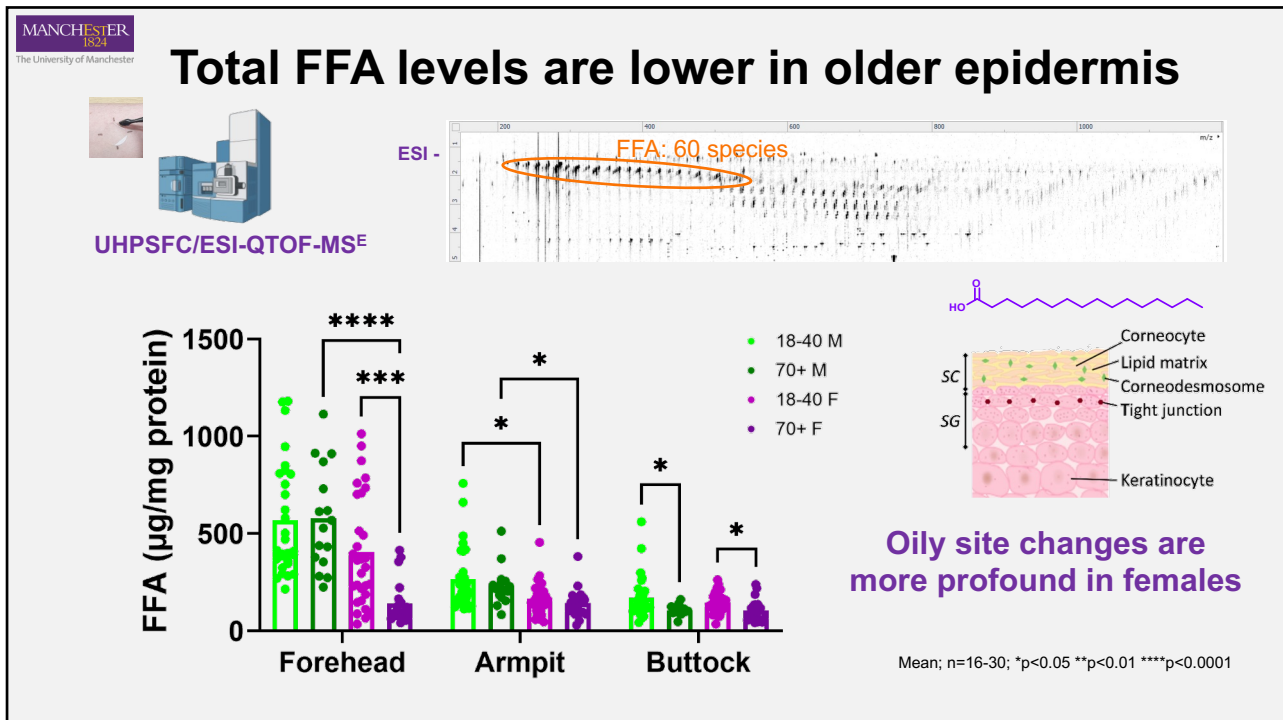
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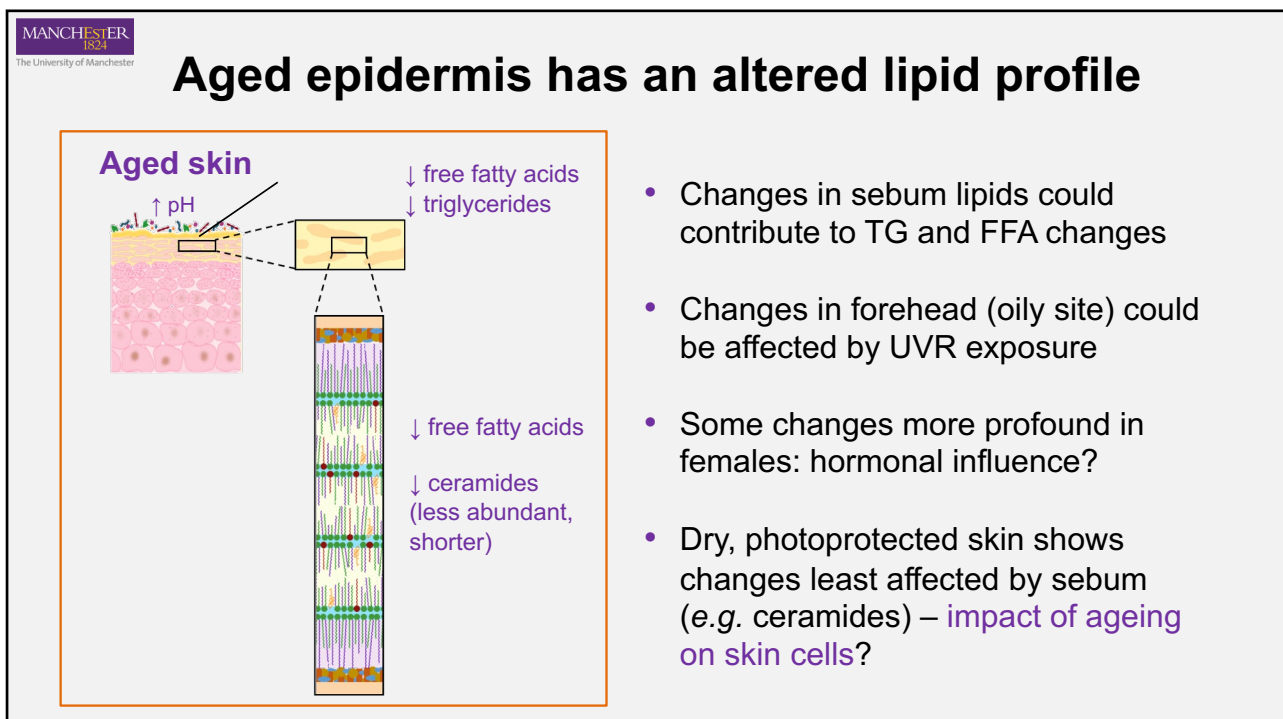
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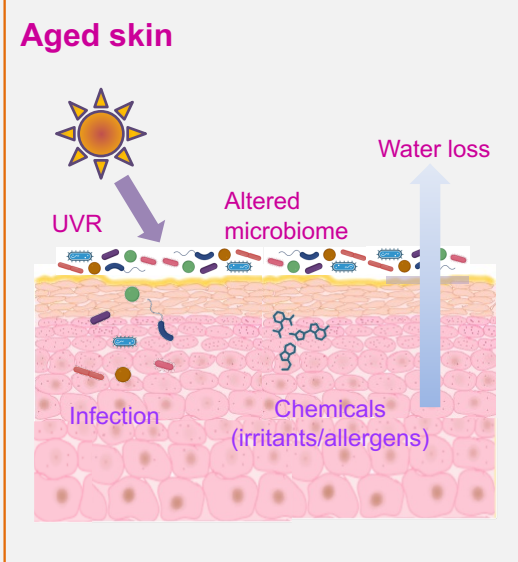


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**What is the potential impact on aged skin?**



**Aged skin**

The diagram illustrates the impact of various factors on aged skin. A sun icon labeled 'UVR' points to the skin surface. An arrow labeled 'Water loss' points upwards from the skin. A cluster of colorful dots on the surface is labeled 'Altered microbiome'. Inside the skin, a blue dot is labeled 'Infection' and a green dot is labeled 'Chemicals (irritants/allergens)'.

**Impaired barrier function and integrity**

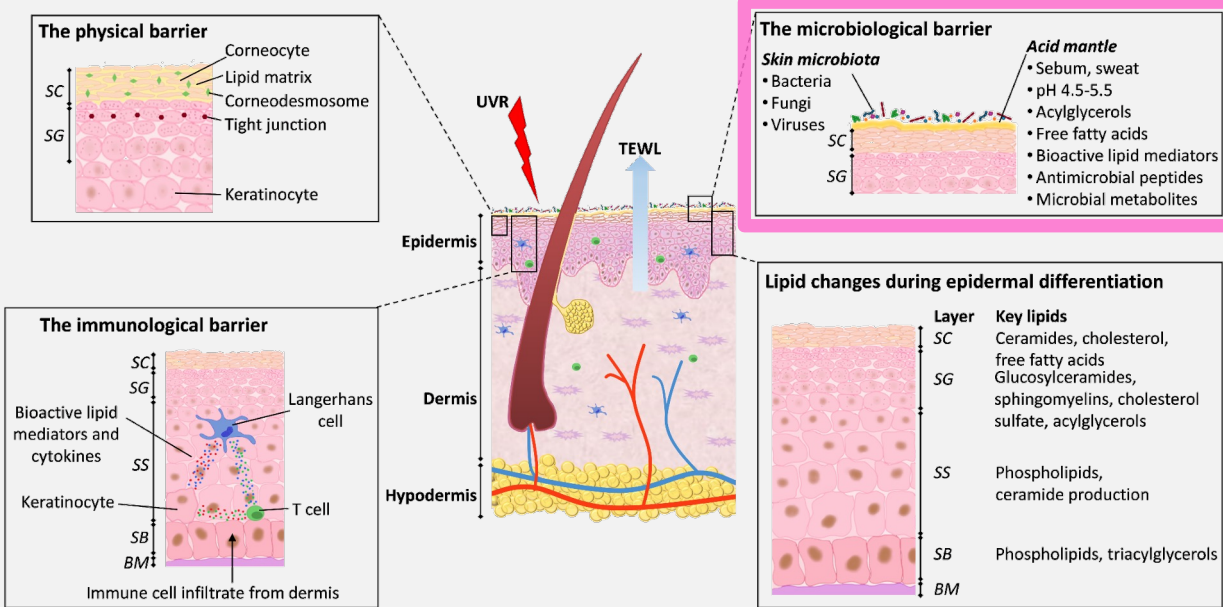
- Changes similar to inflammatory skin conditions (e.g. atopic dermatitis)
- Susceptible to pathogens, chemicals and UVR

**Altered skin microbiome**

- Lipids are both food and antimicrobial agents, and regulate pH
- Microbiota may contribute to epidermal lipid changes

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**Lipids are involved in all aspects of the skin barrier**



The diagram shows a cross-section of the skin with layers labeled SC (Stratum Corneum), SG (Stratum Granulosum), SS (Stratum Spinosum), SB (Stratum Basale), and BM (Basement Membrane). The layers are divided into Epidermis (SC, SG, SS, SB) and Dermis (SS, SB). The Hypodermis is shown below the Dermis.

**The physical barrier**

- Corneocyte
- Lipid matrix
- Corneodesmosome
- Tight junction
- Keratinocyte

**The microbiological barrier**

**Skin microbiota**

- Bacteria
- Fungi
- Viruses

**Acid mantle**

- Sebum, sweat
- pH 4.5-5.5
- Acylglycerols
- Free fatty acids
- Bioactive lipid mediators
- Antimicrobial peptides
- Microbial metabolites

**Lipid changes during epidermal differentiation**

| Layer | Key lipids                                                            |
|-------|-----------------------------------------------------------------------|
| SC    | Ceramides, cholesterol, free fatty acids                              |
| SG    | Glucosylceramides, sphingomyelins, cholesterol sulfate, acylglycerols |
| SS    | Phospholipids, ceramide production                                    |
| SB    | Phospholipids, triacylglycerols                                       |
| BM    |                                                                       |

**The immunological barrier**

- Bioactive lipid mediators and cytokines
- Langerhans cell
- T cell
- Keratinocyte
- Immune cell infiltrate from dermis

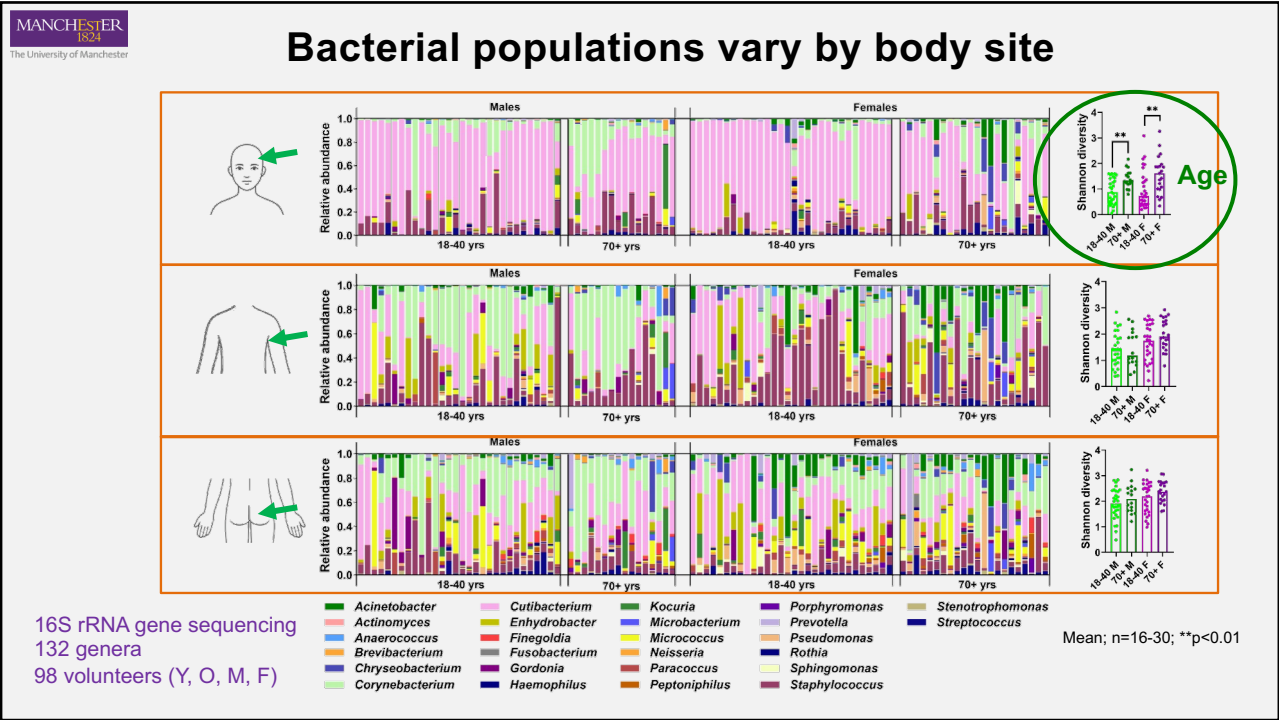
Other labels in the diagram include UVR (ultraviolet radiation), TEWL (transepidermal water loss), and Dermis.

Nicolaou and Kendall (2024) *Pharmacology and Therapeutics*

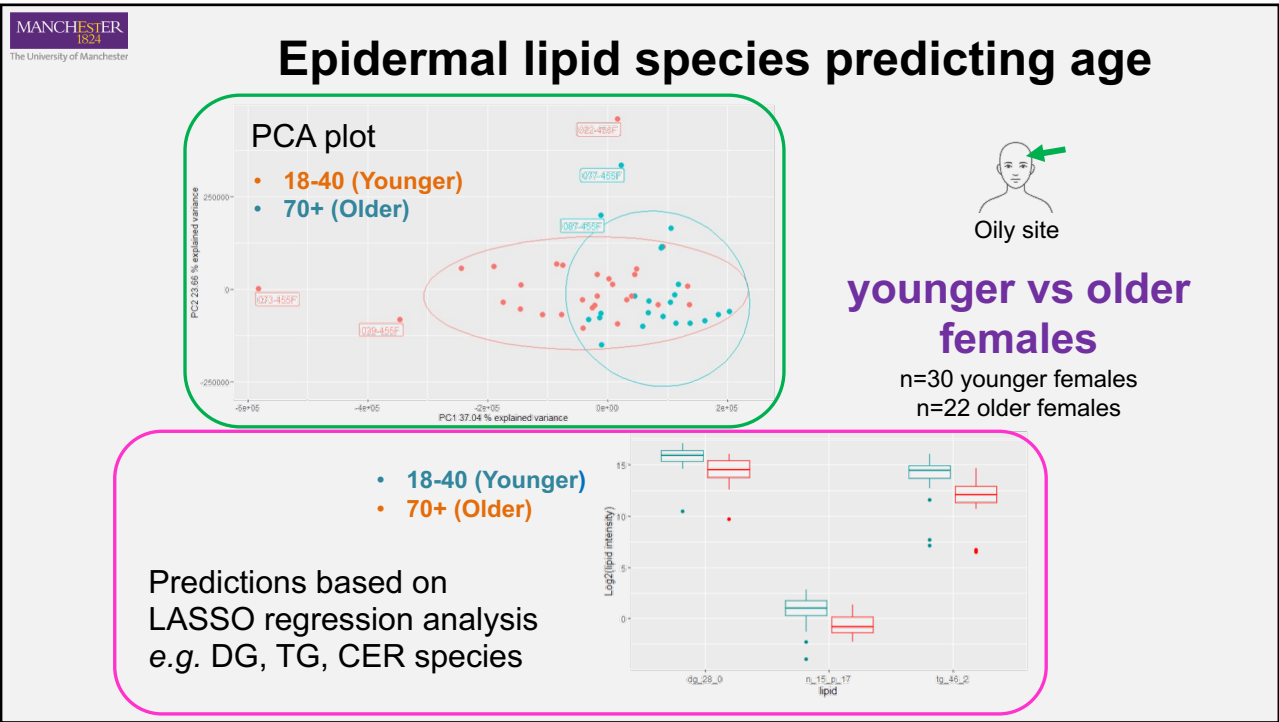
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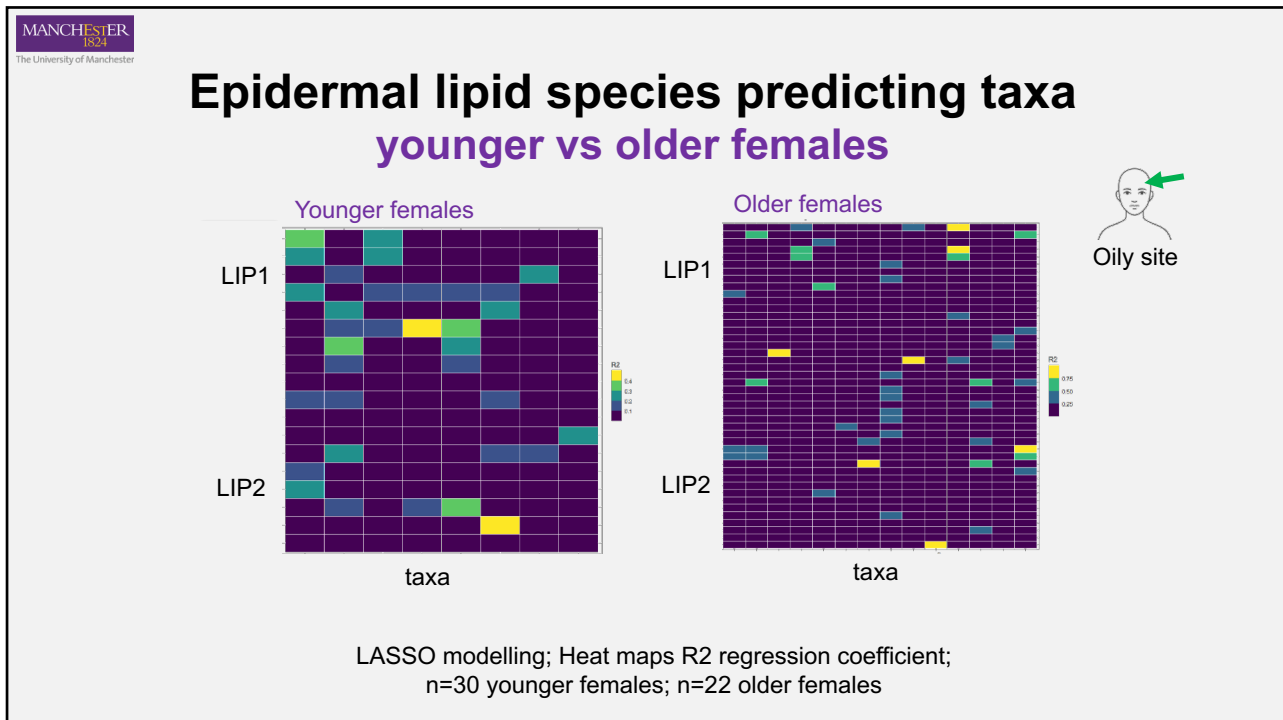
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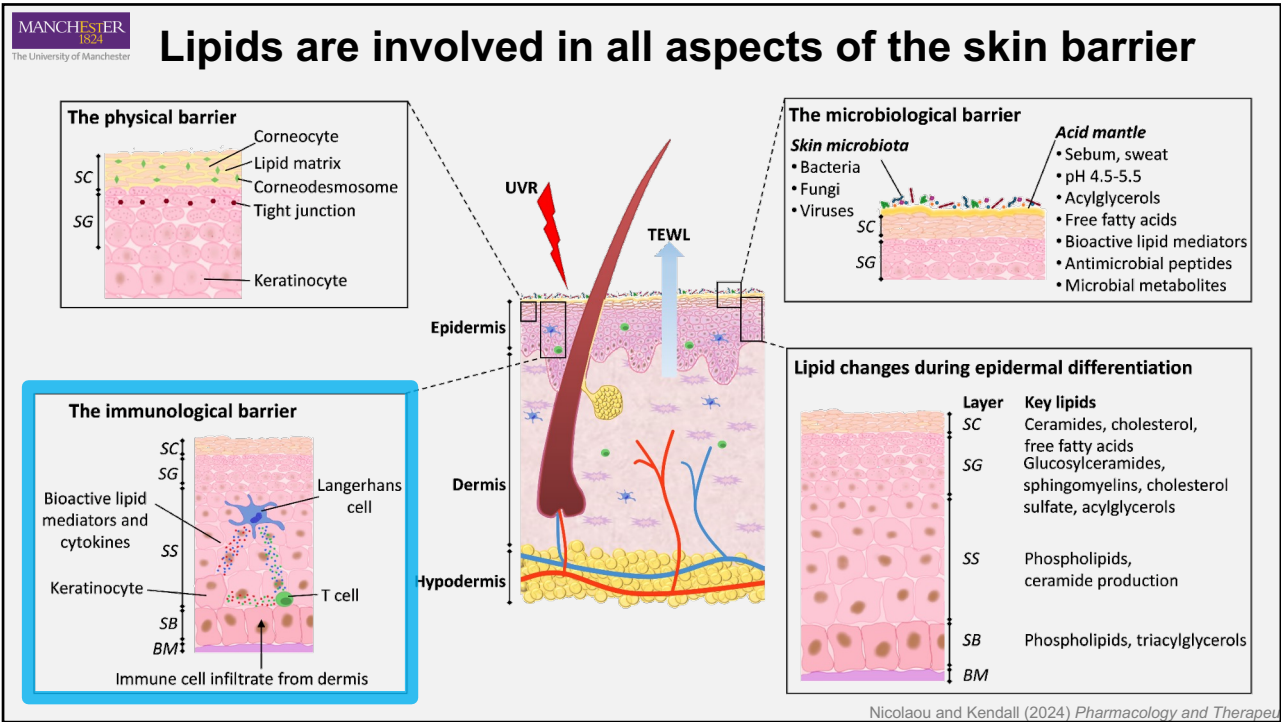
**Lipids and microbiota in aged skin**

**Age-related changes to the lipidome and microbiota**

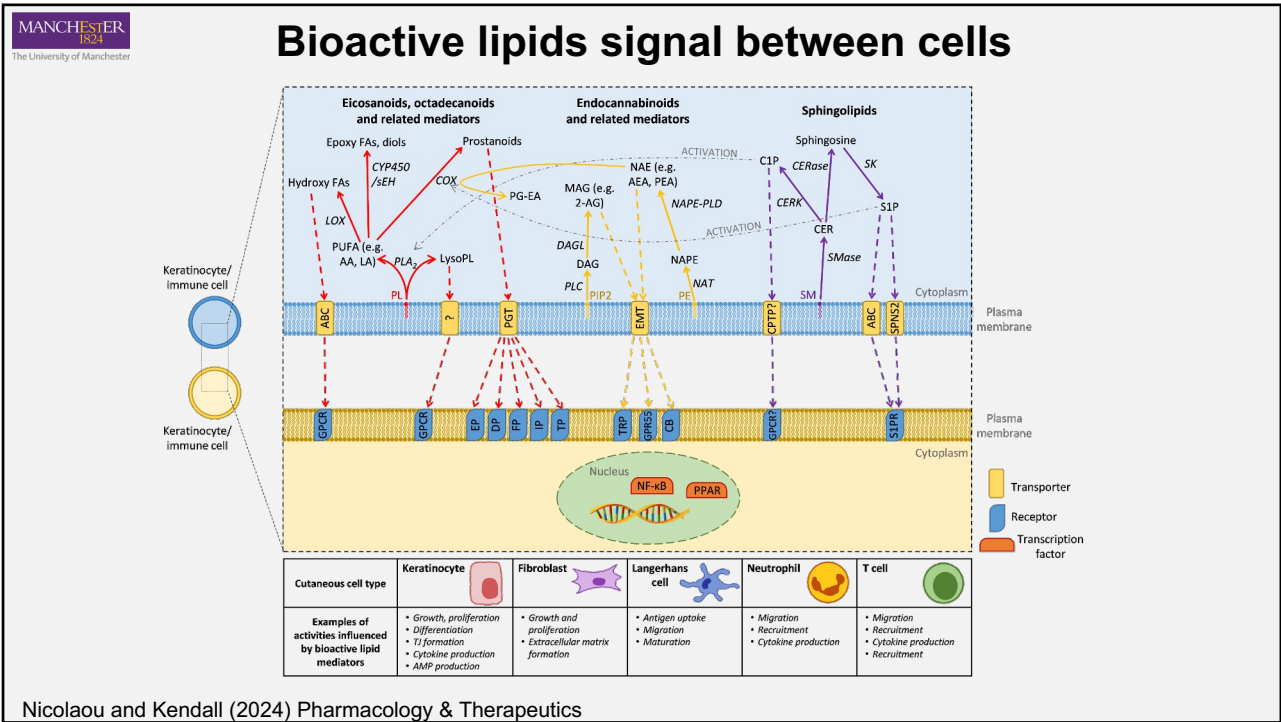
- Relative abundance of main taxa altered in older skin
- Changes in lipid species correlate with changes in the microbiota

Are these changes causative or consequence?  
Are they reflected in different body sites?  
Differential production of antimicrobial and nutritional lipids?  
What are the consequences for the aged epidermis?  
**How do these changes affect the immunological barrier?**

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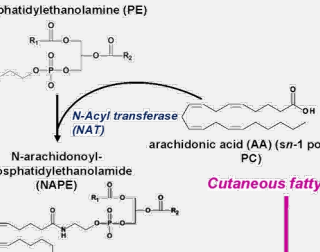


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# Skin produces various NEAs which are upregulated in inflammation and implicated in barrier function



phosphatidylethanolamine (PE)

N-Acyl transferase (NAT)

N-arachidonoyl-phosphatidylethanolamide (NAPE)

NAPE-specific phospholipase D (NAPE-PLD)

anandamide (AEA)

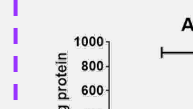
Fatty acid amide hydrolase (FAAH)

arachidonic acid (AA) + ethanolamine

Cutaneous fatty acids

N-Acyl Ethanolamines (NAE)

## Dandruff



AEA

pg/mg protein

Healthy      Dandruff

Kendall et al. IID (2026)

## Barrier disruption



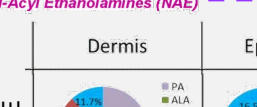
Untreated  
SLS  
UVR

pg/mg protein

Human epidermis; 24 h post 2MED or 2.5% SLS; n=9 volunteers

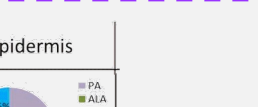
Kendall et al. BJD (2016)

### Dermis



NAE

### Epidermis



Kendall et al. J Inv Derm (2015)

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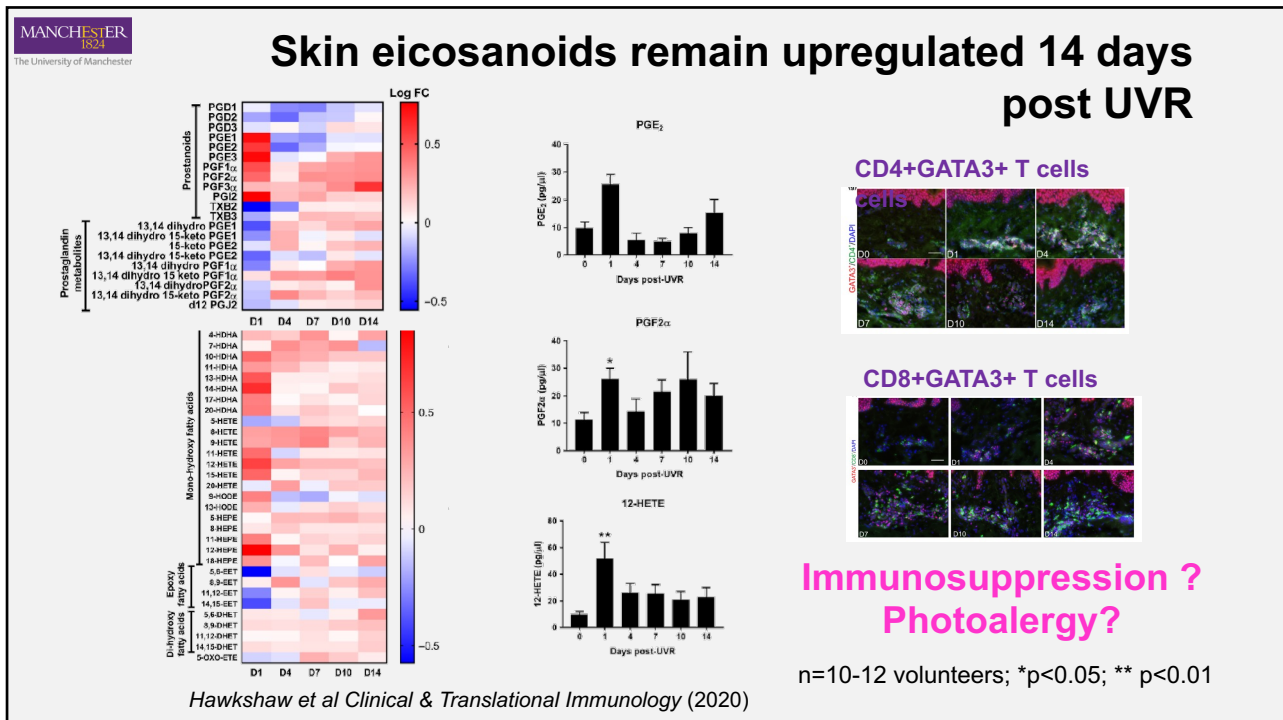
# Lipid mediators of inflammation: the eicosanoids

The diagram illustrates the metabolic pathways of arachidonic acid (20:4n-6), a central eicosanoid, leading to various lipid mediators of inflammation. The pathways are as follows:

- Arachidonic acid (20:4n-6)** is the central starting point.
- COX-1, -2 (PG, TX synthases):** This pathway leads to **PGE<sub>2</sub>** and **TXB<sub>2</sub>** (thromboxane B<sub>2</sub>).
- 5-LOX:** This pathway leads to **5-HETE** (5-hydroxyeicosanoic acid).
- 12-LOX:** This pathway leads to **12-HETE** (12-hydroxyeicosanoic acid).
- 15-LOX:** This pathway leads to **15-HETE** (15-hydroxyeicosanoic acid).
- LOX-LOX:** This pathway leads to **lipoxin B<sub>4</sub>** (lipoxin B<sub>4</sub>).
- CYP450:** This pathway leads to **20-HETE** (20-hydroxyeicosanoic acid).
- non-enzymatic oxidation:** This pathway leads to **8-iso-PGE<sub>2</sub>** (8-iso-PGE<sub>2</sub>) and **9-HETE** (9-hydroxyeicosanoic acid).
- 14,15 EET:** This pathway leads to **14,15 EET** (14,15-epoxyeicosanoic acid).

The diagram shows the chemical structures of these eicosanoids, highlighting the positions of hydroxyl groups and double bonds. The pathways are color-coded: red for COX-1, -2; blue for 5-LOX, 12-LOX, 15-LOX, LOX-LOX, and CYP450; and green for non-enzymatic oxidation.

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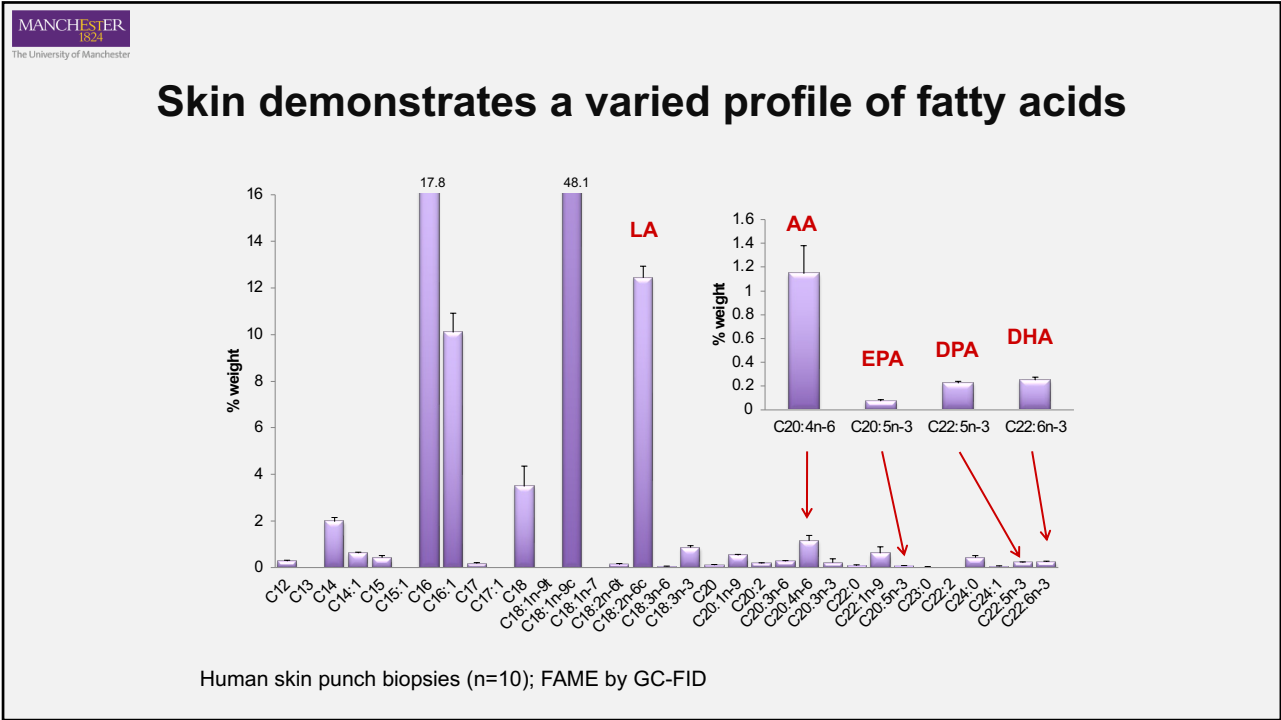


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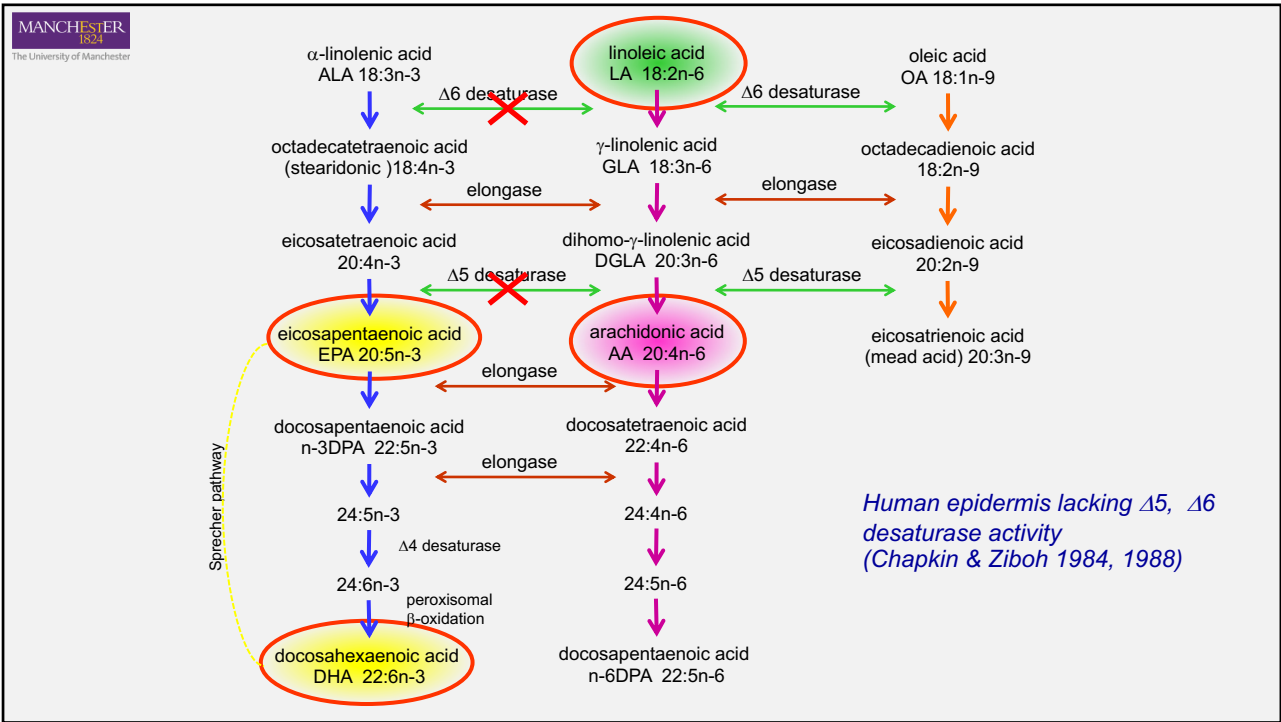
**How can we support the epidermal barrier?**

- Topical treatments (e.g. ceramide-containing creams; emollients)
- **Fatty acid supplementation**
- **Exploring the gut skin-axis**

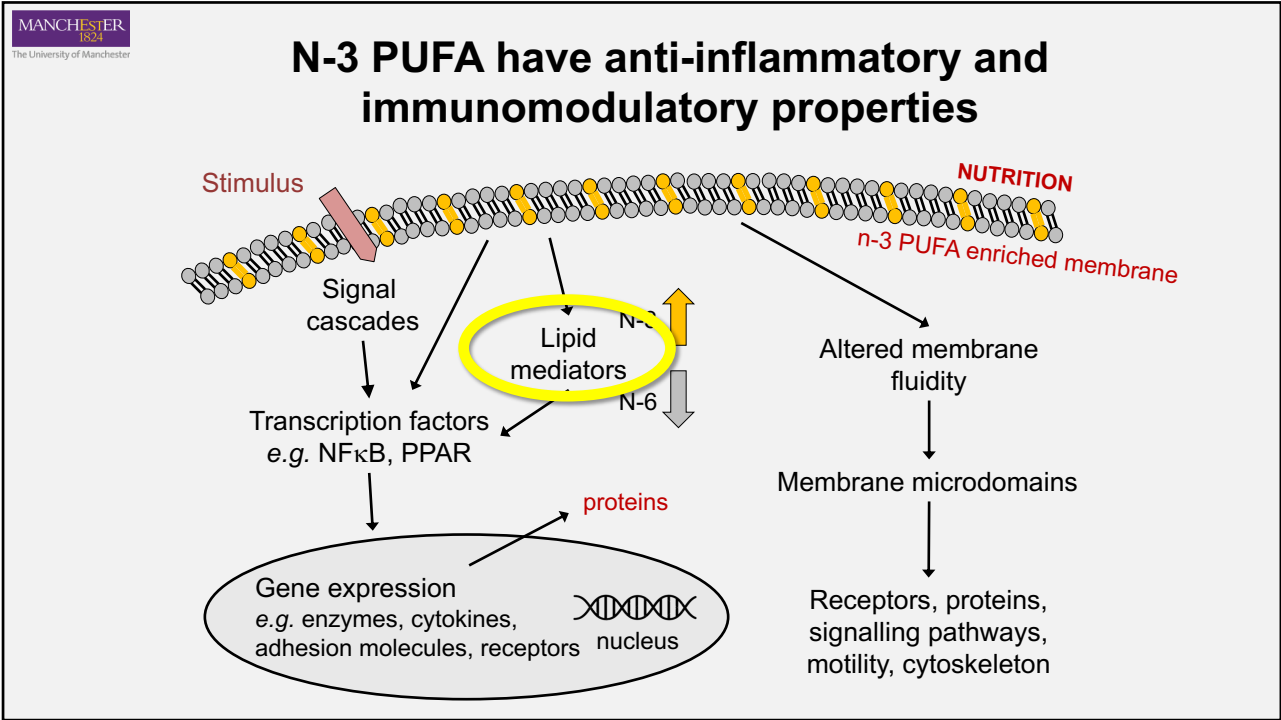
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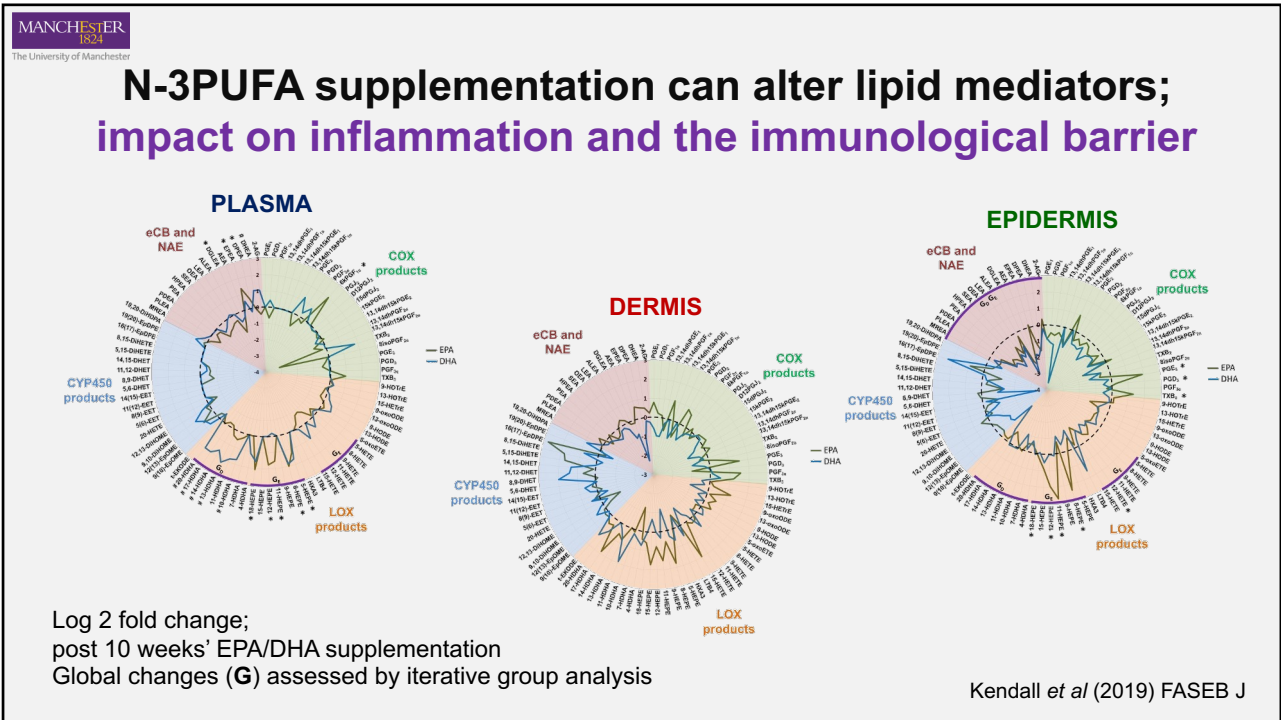
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# Can n-3PUFA alter the sunburn response?

Volunteers randomly assigned to EPA or DHA, 5g per day for 10 weeks:

**EPA capsule**

| FA Type | % of total FA |
|---------|---------------|
| EPA     | ~70           |
| DHA     | ~10           |

**DHA capsule**

| FA Type | % of total FA |
|---------|---------------|
| EPA     | ~10           |
| DHA     | ~75           |

Compliance confirmed with RBC analysis

**EPA Group RBC Analysis**

| FA Type | Pre-EPA | Post-EPA |
|---------|---------|----------|
| AA      | ~11     | ~12      |
| EPA     | ~1      | ~5       |
| DPA     | ~1      | ~4       |
| DHA     | ~4      | ~5       |

**DHA Group RBC Analysis**

| FA Type | Pre-DHA | Post-DHA |
|---------|---------|----------|
| AA      | ~11     | ~12      |
| EPA     | ~1      | ~1       |
| DPA     | ~1      | ~2       |
| DHA     | ~4      | ~8       |

Small areas of photoprotected upper buttock skin were exposed to UVR at 3 times the minimum erythral dose:

UVR (mJ/cm<sup>2</sup>)

Biopsies taken after 24 h and 72 h, analysed for lipid content and immune cell profiles:

UPLC/ESI-MS/MS

No UVR      24h post-UVR

Kendall *et al.* (2019). *FASEB*. 33:13014-27

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# Systemic n-3PUFA alter UV-induced epidermal lipids

The figure displays two network diagrams illustrating the systemic n-3PUFA (EPA and DHA) altering UV-induced epidermal lipids. The diagrams show the relationships between various lipid species, with nodes representing lipids and edges representing their interactions. The color scale indicates the log2 fold change (log2 FC) of the lipids, ranging from -6 (yellow) to 6 (purple).

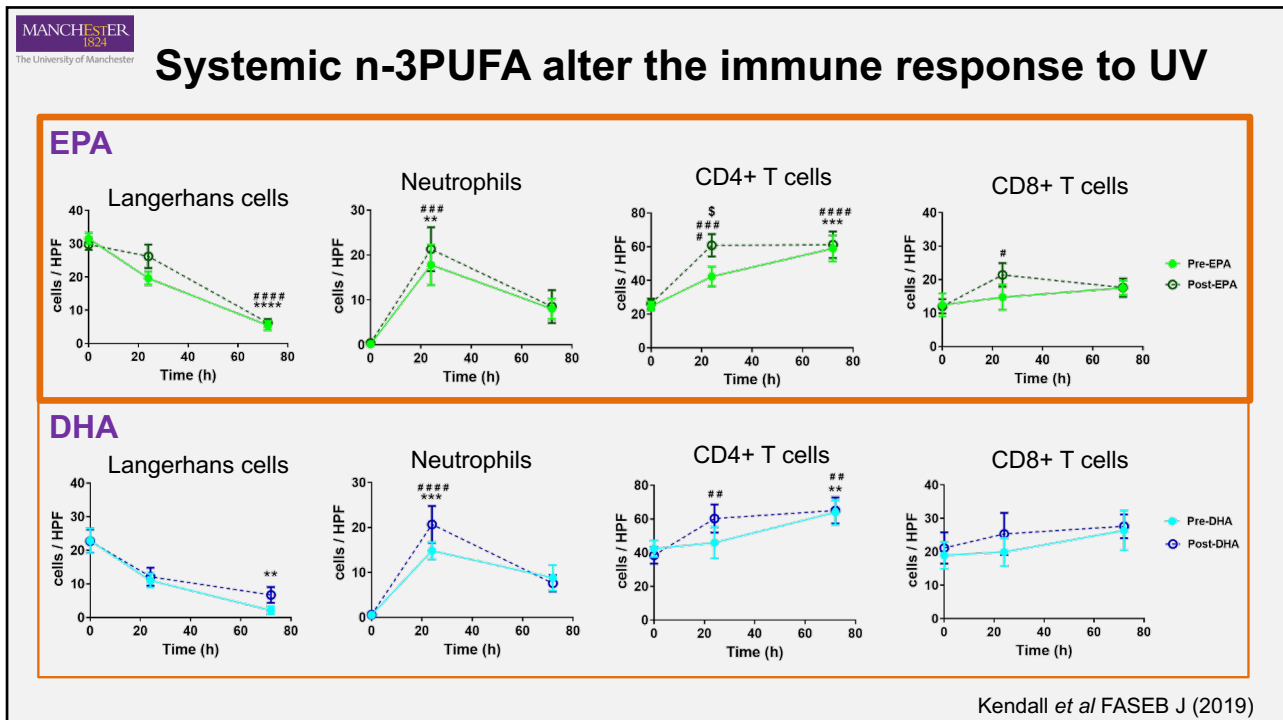
**EPA Network:** The central node is EPA. It is connected to a large number of other lipid species, including DHA, ALA, AA, DGLA, LA, and various other fatty acids and lipids. The network shows a complex web of interactions, with many nodes having high log2 FC values (purple).

**DHA Network:** The central node is DHA. It is connected to a large number of other lipid species, including EPA, ALA, AA, DGLA, LA, and various other fatty acids and lipids. The network shows a complex web of interactions, with many nodes having high log2 FC values (purple).

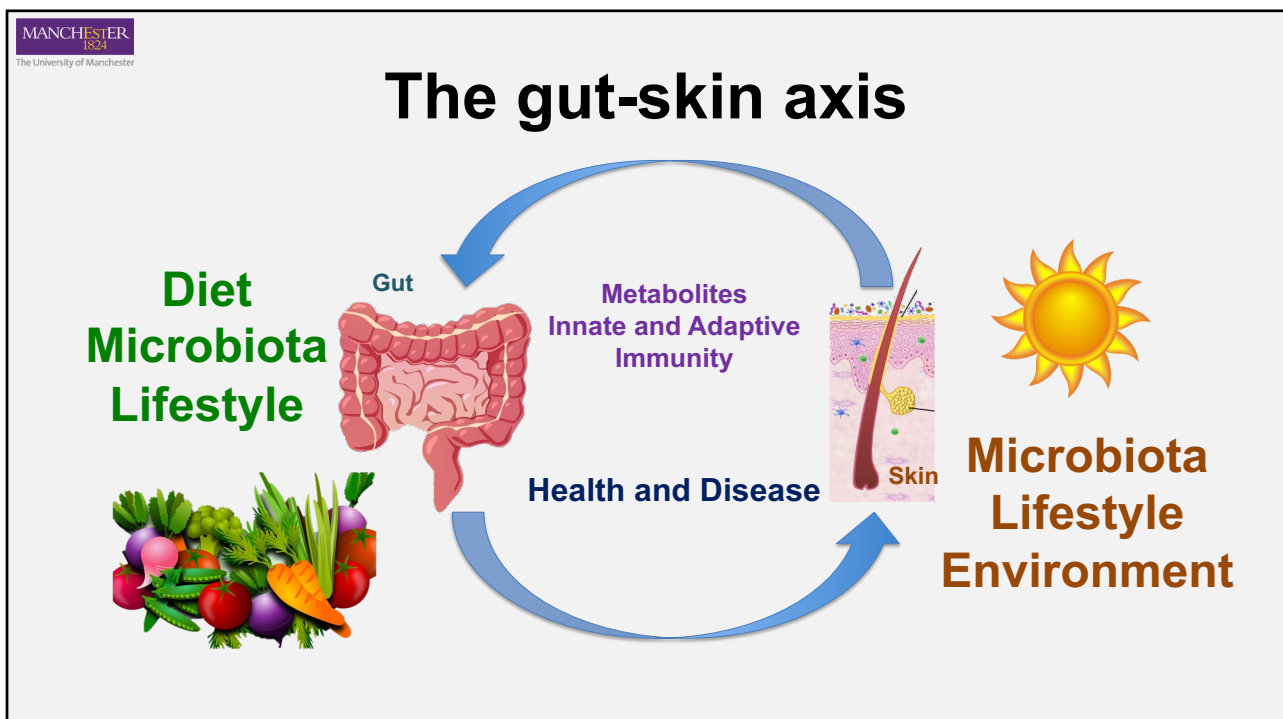
Both networks include a color scale for log2 FC, ranging from -6 (yellow) to 6 (purple). The scale is shown at the bottom of each network.

Kendall *et al* FASEB J (2019)

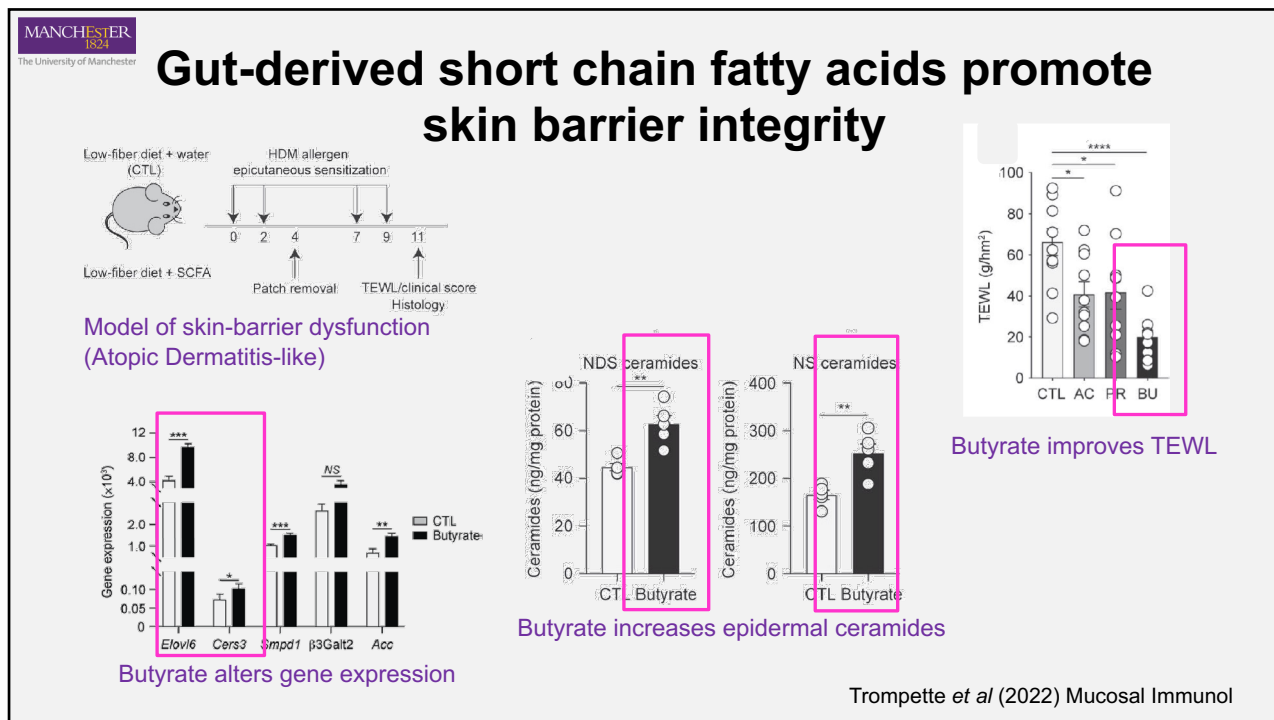
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**Skin barrier lipids – what's next?**

- Understand how **lipid networks** contribute to skin reactions in skin disease or systemic conditions with skin manifestations
- Develop *in vitro* and *in silico* models to study mechanisms and support **product development**
- Understand the functionality of skin **microbiota** and role of **microbial lipids** in skin health and disease
- Develop **interventions** specific to the needs of skin across different age groups, in both males and females

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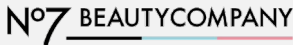
  
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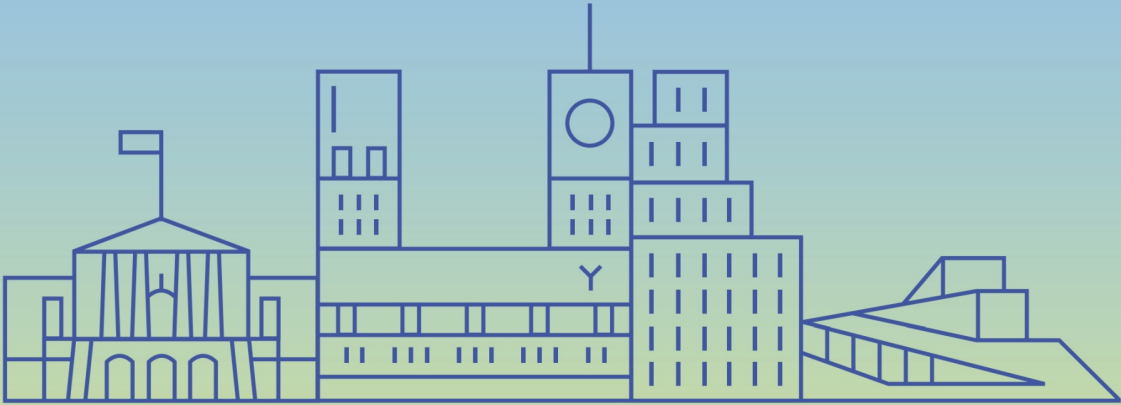
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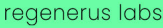
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