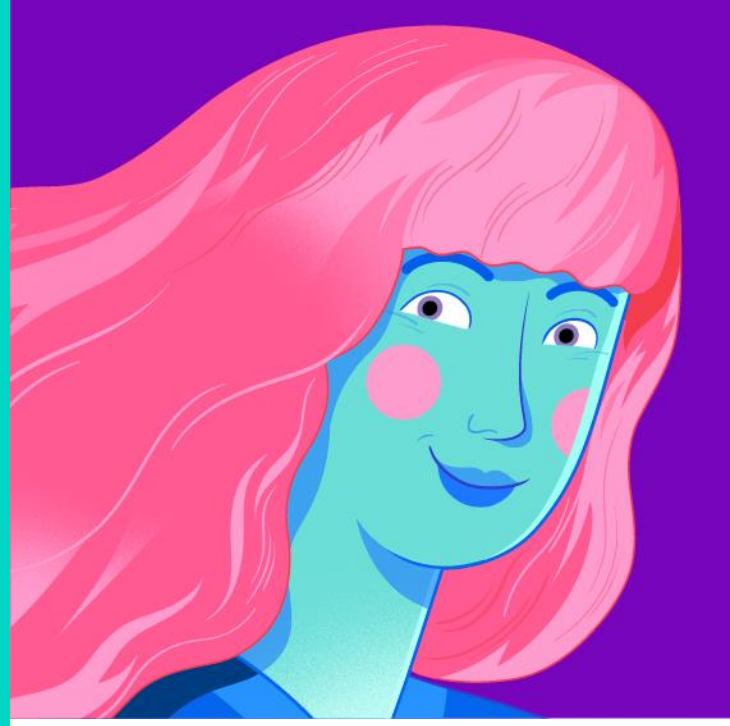
The Microbiome and Skin Aging



November 2022

Michael Hoptroff

Unilever

Microbiome at Unilever

Microbiomics Capability

2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2022

Capability

Underarm & Skin Microbiome

TNO innovation for life

Unilever

Underarm, Skin and Scalp Microbiome

Technology Strategy Board
Driving Innovation

Unilever

University of Glasgow

University of Liverpool

Harmonised Microbiome Data Pipeline

eagle genomics

dime2 Cytoscape jmp R Microsoft Azure

MIF OMICS Unilever University of Liverpool BBSRC

Baby Microbiome

The PEARL Study Pregnancy and Beyond BBSRC

Aging

SMiHA Skin Microbiome in Healthy Ageing

UK R&D Strategy

Innovate UK Knowledge Transfer Network

Microbiome AI

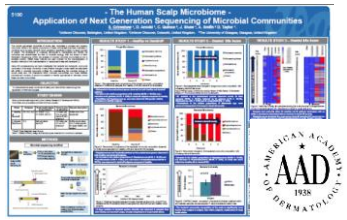
Science & Technology Facilities Council

Insights

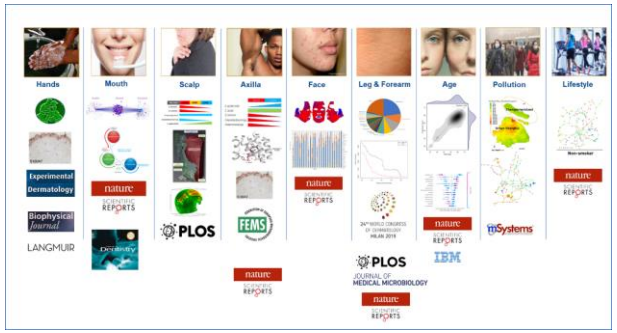
Oral Microbiome

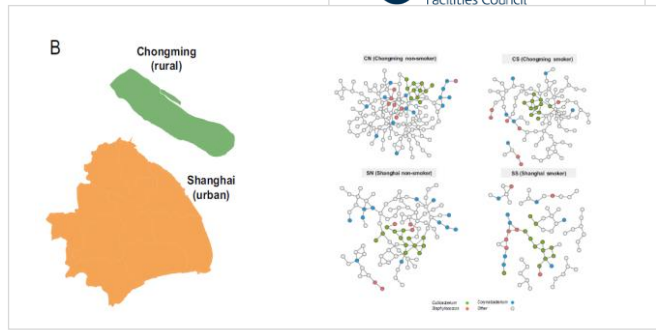
IADR International Association for Dental Research

Scalp Microbiome



AAD American Academy of Dermatology





Partnerships

Global Microbiome Research Network

Market

Unilever

Whole Body Understanding

Microbiome Insight


Hands


Mouth


Scalp


Axilla


Face

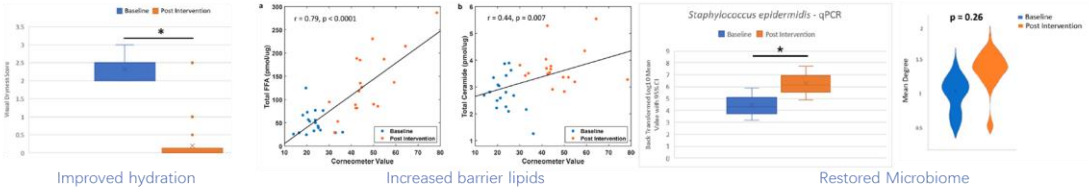

Leg & Forearm


Age


Pollution


Lifestyle

Treatment of Dry Skin (clinical study, n=37)

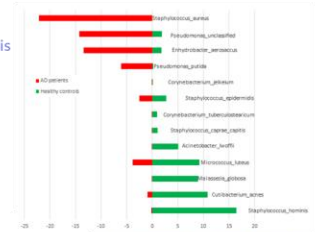


Improved hydration | Increased barrier lipids | Restored Microbiome

scientific reports https://doi.org/10.1038/s41598-022-09231-8

Atopic Skin (clinical study, n=23)

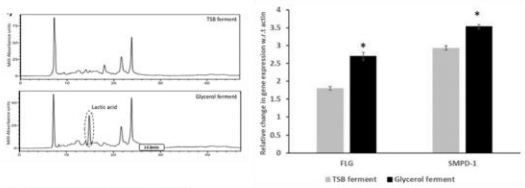
- Elbow, Neck
- Indian population
- Metagenomic analysis



frontiers in Cellular and Infection Microbiology doi: 10.3389/fcimb.2020.570423

Prebiotics to increase lactic acid production

- Increased microbial production of lactic acid
- Increased epidermal gene expression



Experimental Dermatology DOI: 10.1111/exd.14604

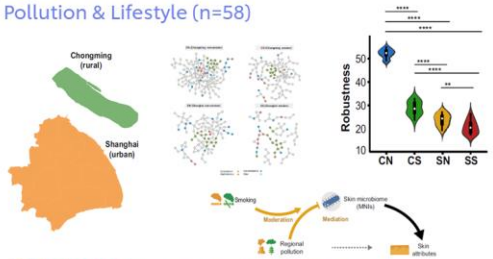
Impact of Preservatives (n=60)

- Lotions & Cleansers
- DMDM Hydantoin
- Iodopropynylbutylcarbamate
- Phenoxyethanol
- Propyl/methyl paraben

C	System A T1vT2	System B T1vT2	System C T1vT2	System D T1vT2
Chao1	p=0.69	p=0.66	p=0.085	p=0.22
Faith's PD	p=0.60	p=0.63	p=0.25	p=0.39
Shannon	p=0.41	p=0.88	p=0.75	p=0.19

PLOS ONE https://doi.org/10.1371/journal.pone.0254172

Pollution & Lifestyle (n=58)

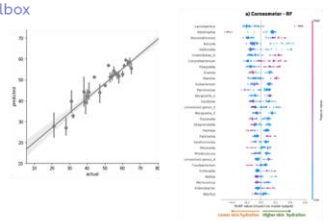


mSystems https://doi.org/10.1128/mSystems.00319-21

Microbiome AI (n=164)

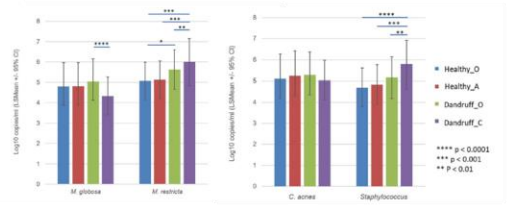
Hartree Centre Science & Technology Facilities Council IBM

- "Explainable" AI toolbox
- 2 x Clinicals
- Dry skin
- Age
- Smoking
- Menopause



scientific reports https://doi.org/10.1038/s41598-021-83922-6

Dandruff Microbiome (n=120)



PLOS ONE https://doi.org/10.1371/journal.pone.0225796

Unilever

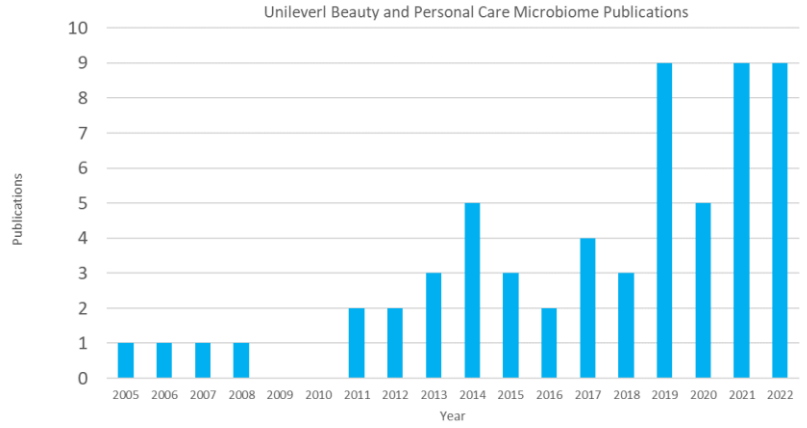
Microbiome Science

Microbiome Insight

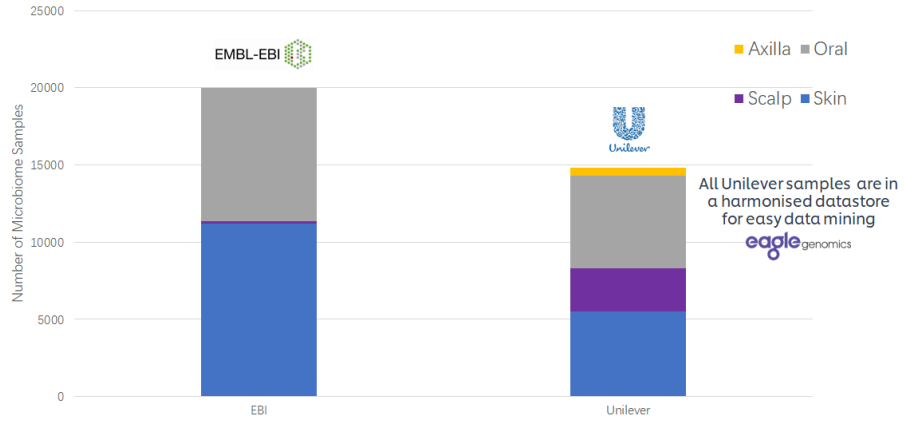
More than 30 conference speeches

Over 65 publications

More than 100 patents



Our data in context:



Biotechnology and Biological Sciences Research Council

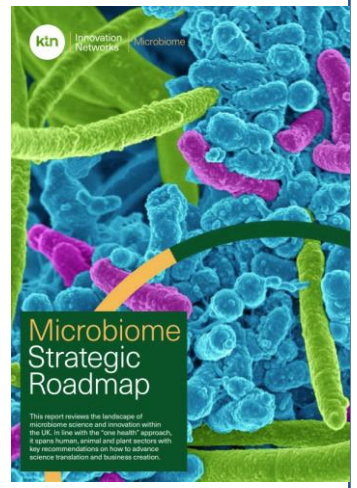
LIDo London Interdisciplinary Doctoral Programme @ UCL, KCL, QMUL, Birkbeck, LSHTM, RVC

SMiHA Skin Microbiome in Healthy Ageing

University of Liverpool

Microbiome Innovation Centre
A global opportunity for Industry, for Research, for the Future

Quadram Institute
Science Health Food Innovation



Industrial Advisory Panel

- Current cohort of 62 students.
- New: 35 four-year studentships (Oct 2022)
  - 11 PhD in 2022,
  - 12 PhD in 2023,
  - 12 PhD in 2024,

What is Skin (...from a microbes perspective ☺)

Microbial Ecology

A place to live

Chemical

- Aridity
- pH
- Osmolarity
- O_2/AnO_2
- HLB
- Host Antimicrobials
- UV

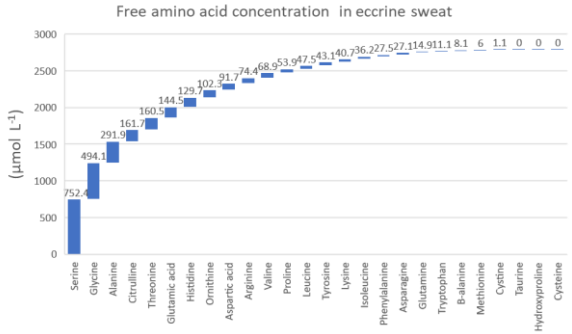
Physical

- Substrate
- XYZ constrained
- °C
- Desquamation
- Turnover
- Stability

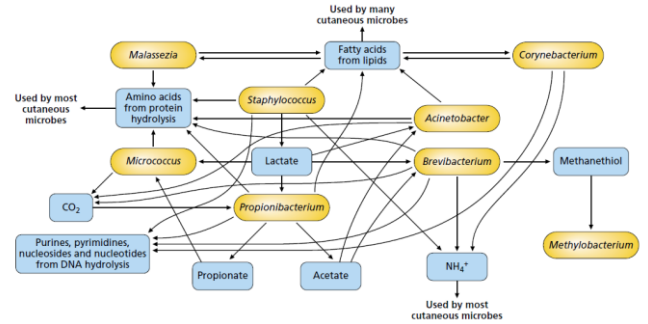
"it's the environment, stupid"

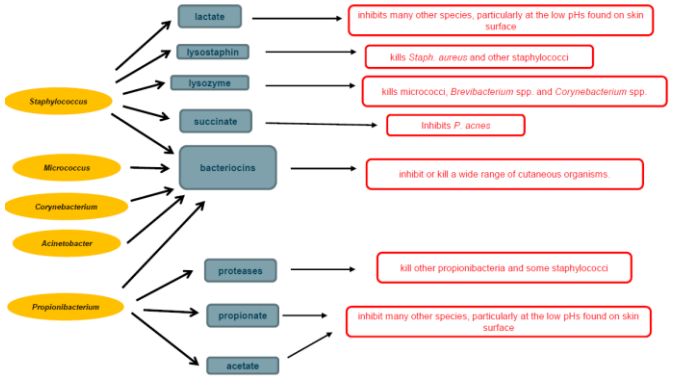
A source of food

CLASS OF NUTRIENT	COMPOUND	SOURCE
Carbon/energy source	Glucose	Sweat; hydrolysis of glycoproteins
	Ribose	Hydrolysis of nucleic acids
	Glycerol	Lipid hydrolysis
	Amino acids	Hydrolysis of proteins; sweat
	Fatty acids	Stratum corneum; sweat; hydrolysis of lipids; sebum, microbes
	Lactic acid	Sweat; microbes
Nitrogen source	NH_4^+	Sweat; microbes
	Amino acids	Sweat
	Urea	Sweat
	Uric acid	Sweat
Essential amino acids	Amino acids	Hydrolysis of proteins; sweat
Phosphorus	Phosphate	Hydrolysis of nucleic acids; sweat
Vitamins and growth factors	Biotin, thiamine, riboflavin, nicotinic acid, pyridoxine, inositol, ascorbic acid, p-aminobenzoate	Sweat
	Vitamin E	Sebum
Micronutrients	Na^+, K^+, Mg^{2+}, Cl^-	Sweat; dead keratinocytes; interstitial fluid



A home shared with friends & enemies





"External" Stressors

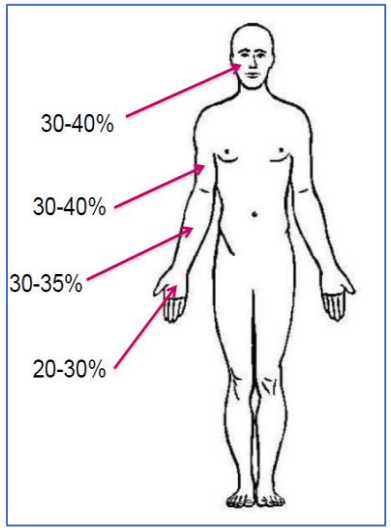
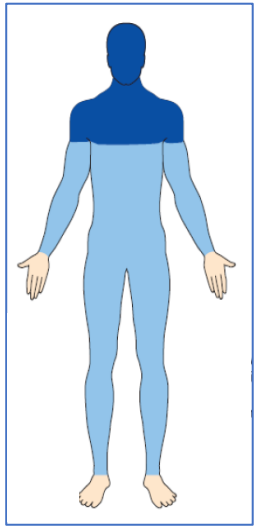
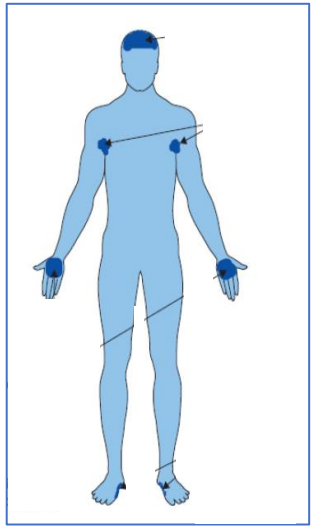
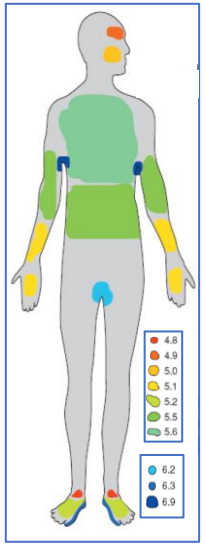
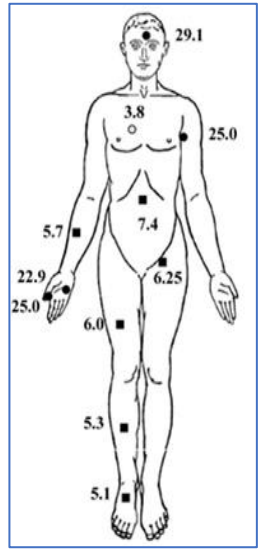
Inflammation | Injury | Immune response | Climate | Product use | Lifestyle etc

Wilson, Bacteriology of Humans; 2008
Harker & Harding, Amino acid composition, including key derivatives of eccrine sweat; 2013
Wilson, The Human Microbiota in Health & Disease, 2018
Baker & Wolfe, Physiological mechanisms determining eccrine sweat composition; 2020

Unilever

Human Skin – Multiple Environments in One

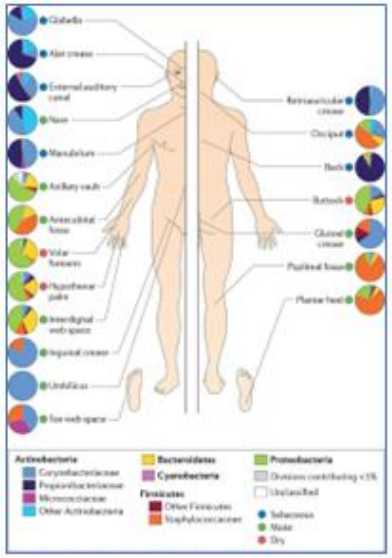
Body Site & Environment

	Water	Sebum	Sweat	pH	AMP
					
Microbiome Balance (+)	Hydration	Nutrients	Nutrients	Promotes Commensals	Promotes Commensals
(–)	Osmolarity	Antimicrobial	pH	Discourages Pathogens	Discourages Pathogens

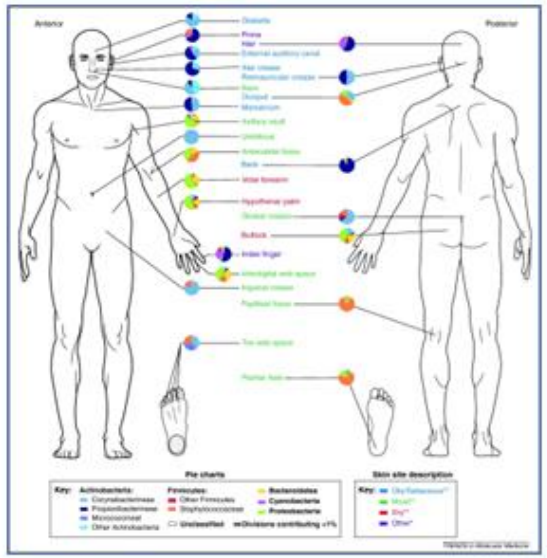
Bacteriology of Humans; Prof. Michael Wilson, 2008

Environment & Microbiome

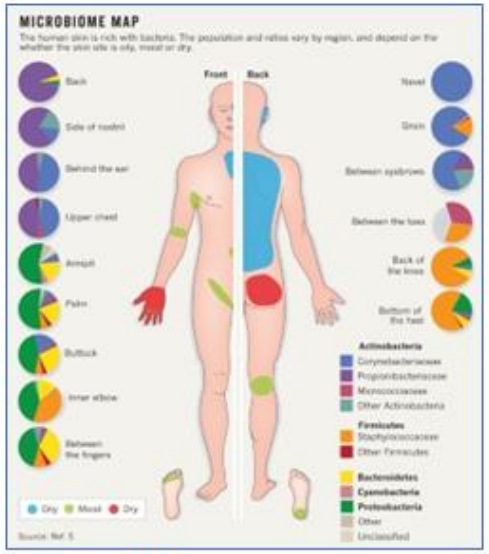
Body Site & Environment



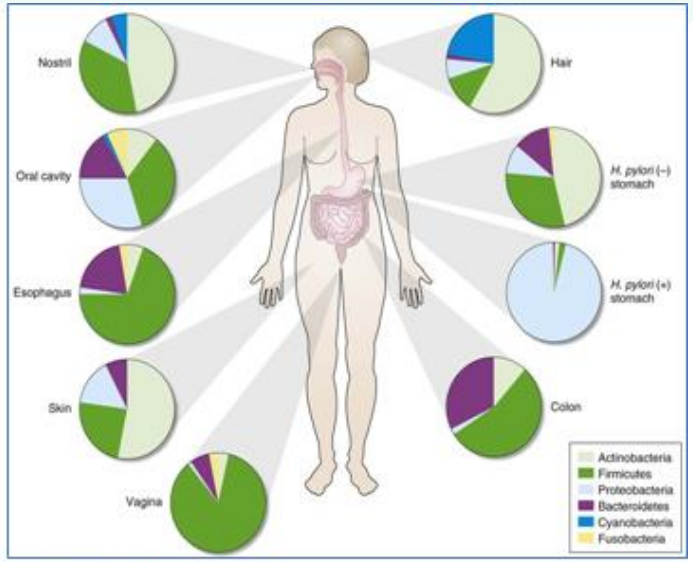
Grice and Segre, 2011



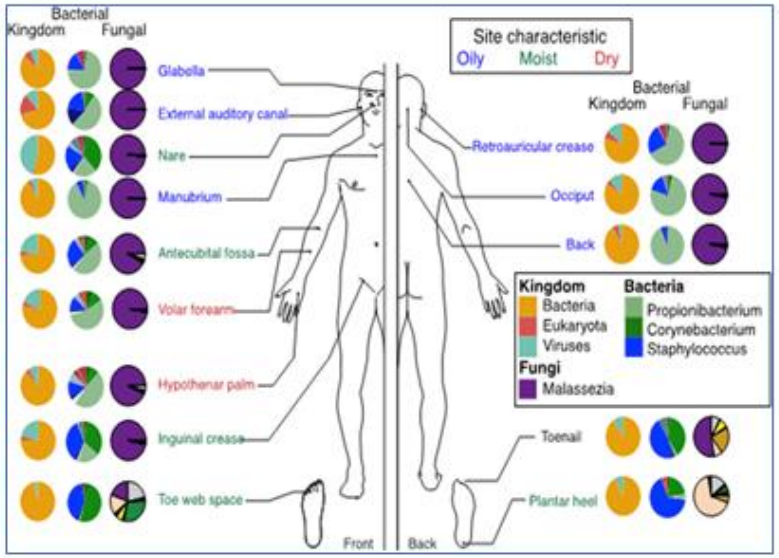
Kong, 2011



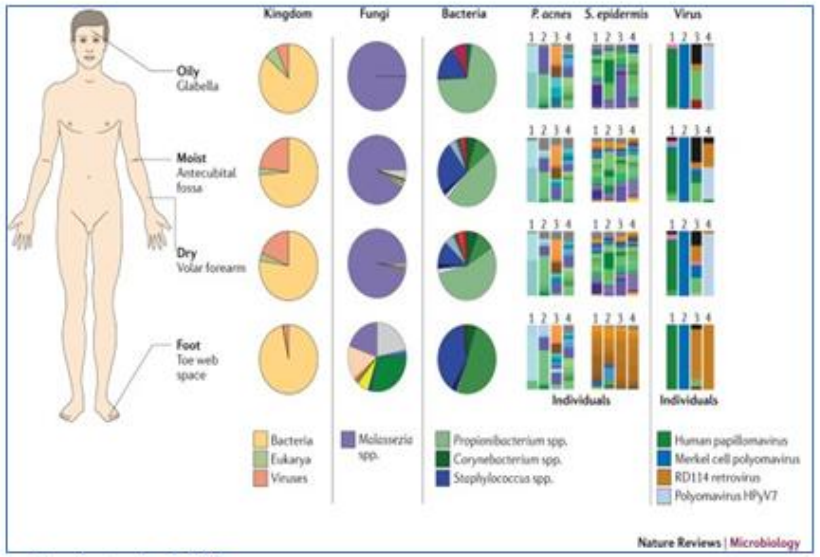
Trivedi, 2012



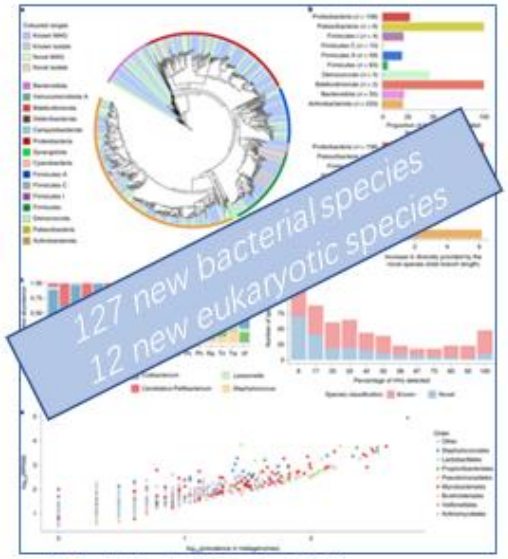
Cho and Blaser, 2012



Oh et al, 2014, Kong and Segre, 2017

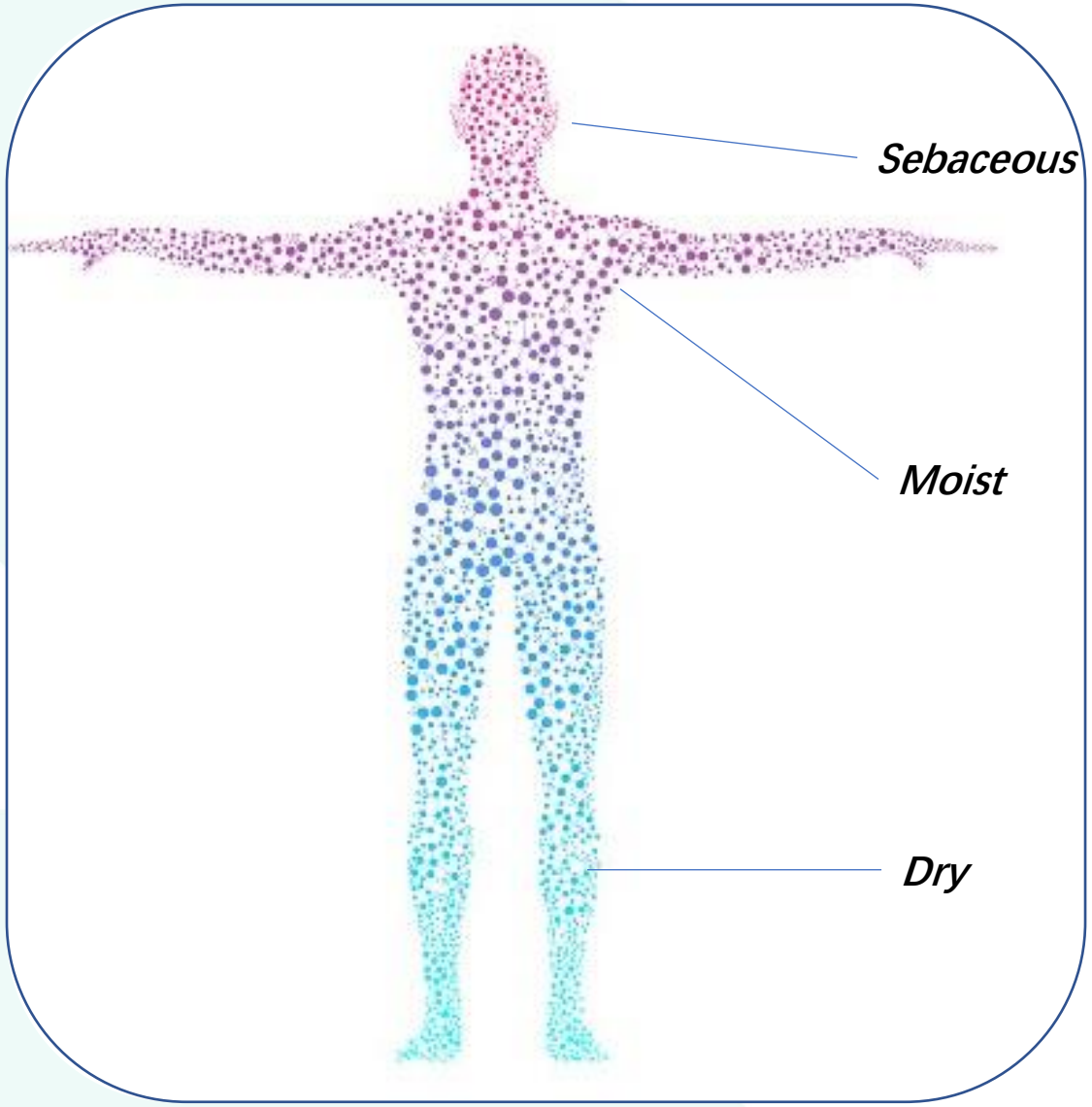


Byrd et al., 2018



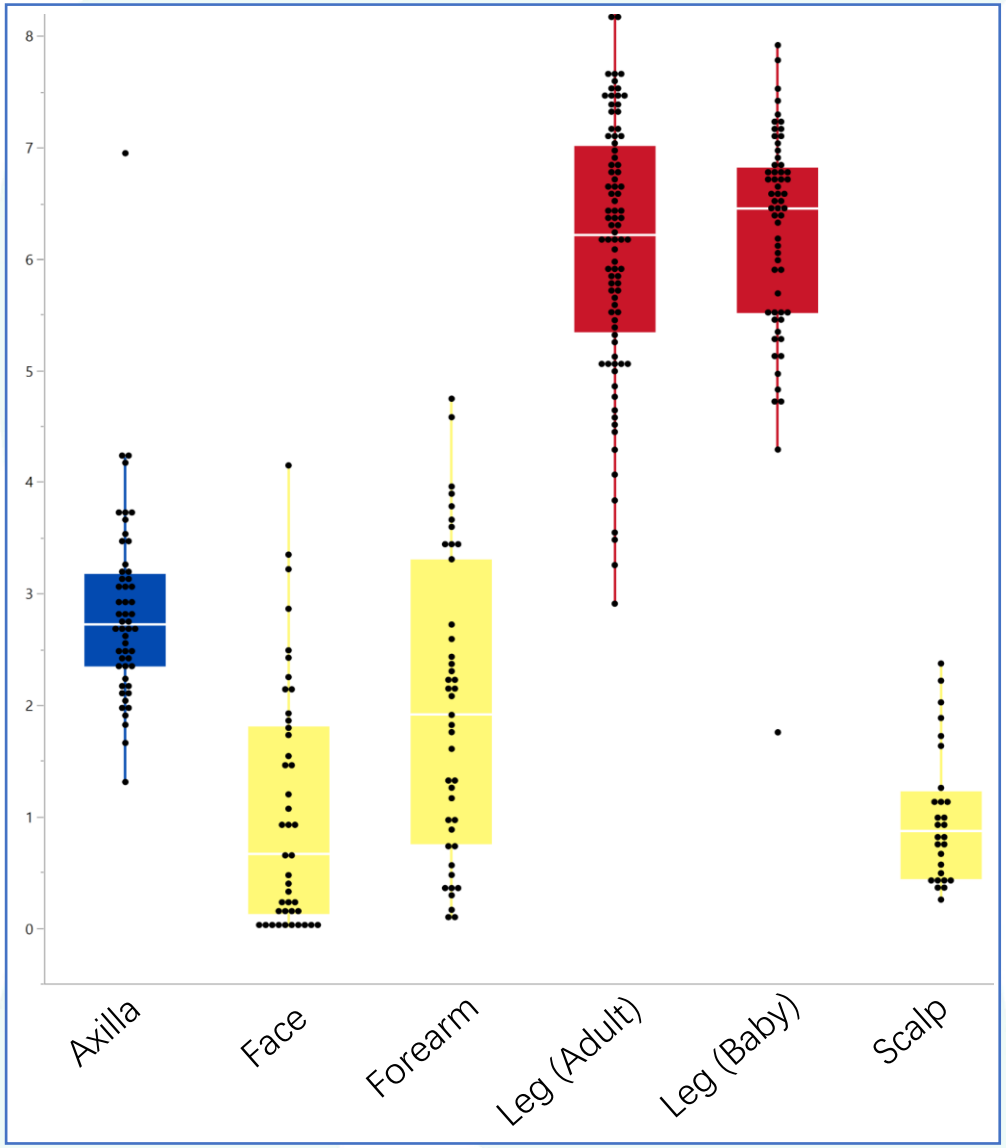
Saheb Kashaf et al., 2021

Body Sites – Unilever Data

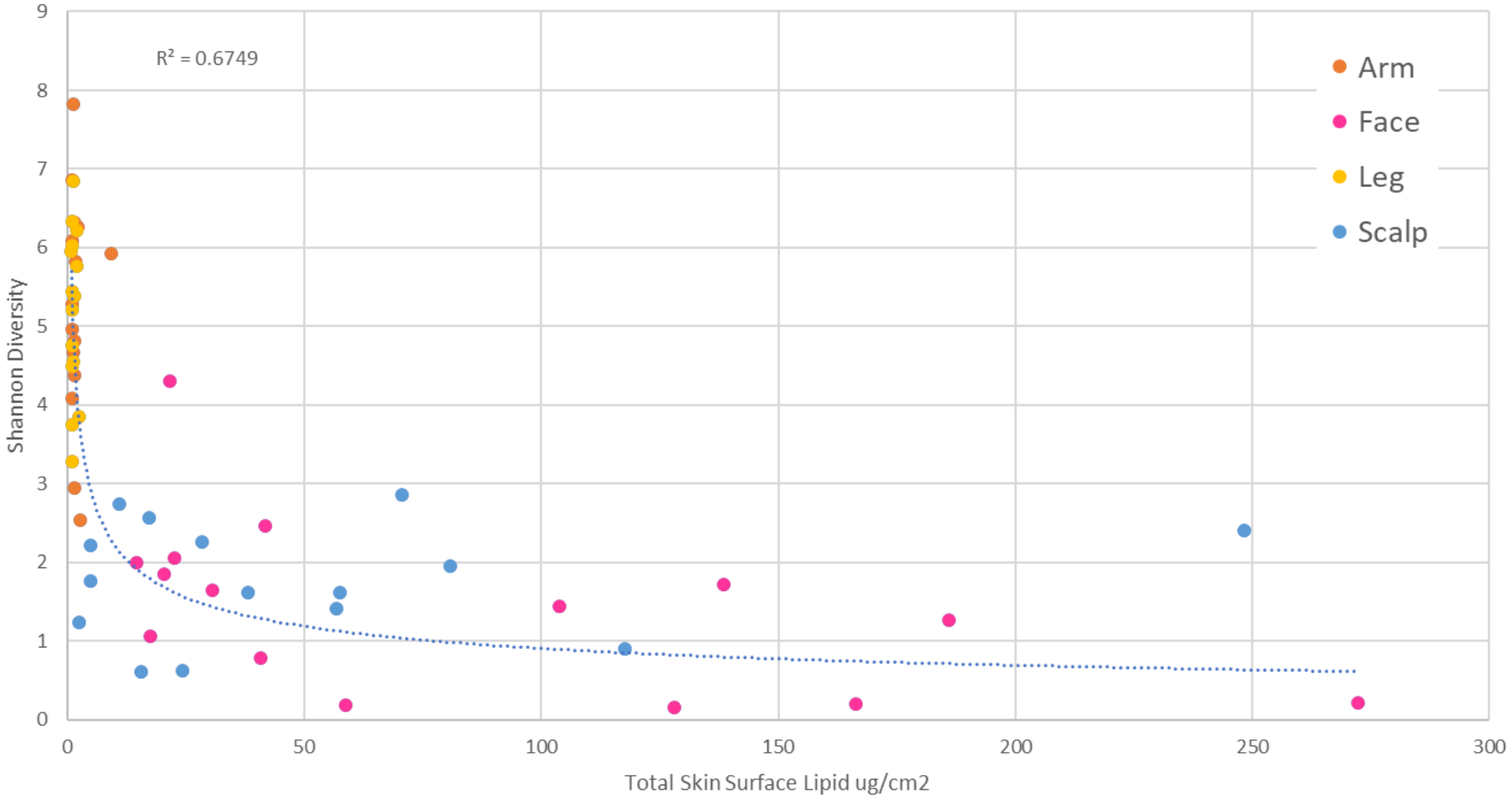


331 subjects

Shannon Diversity – Richness and Evenness

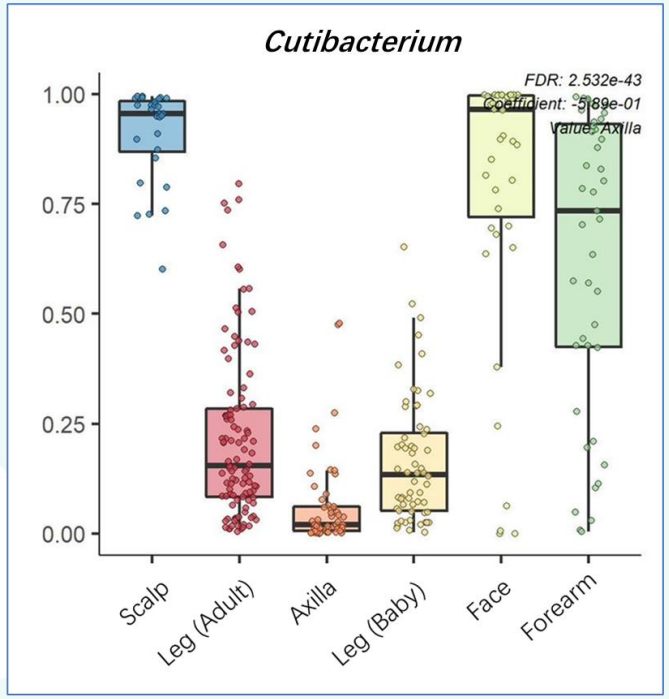


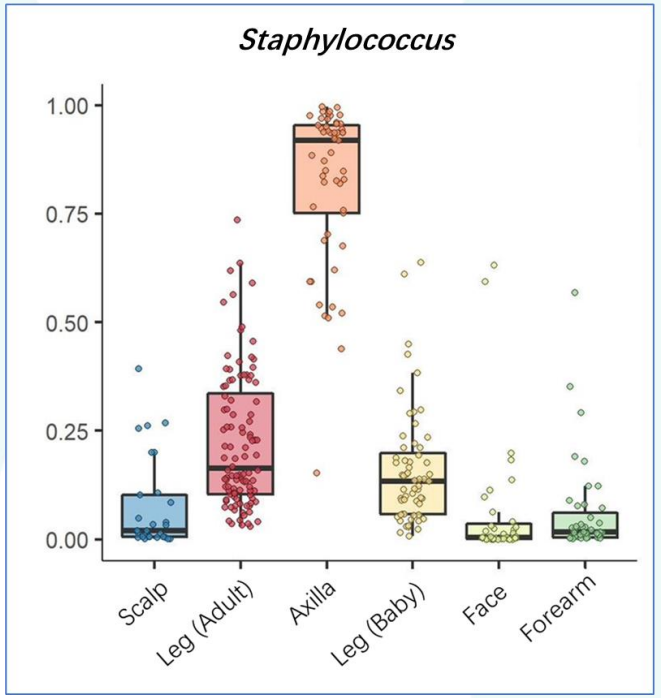
Body Sites – Alpha Diversity

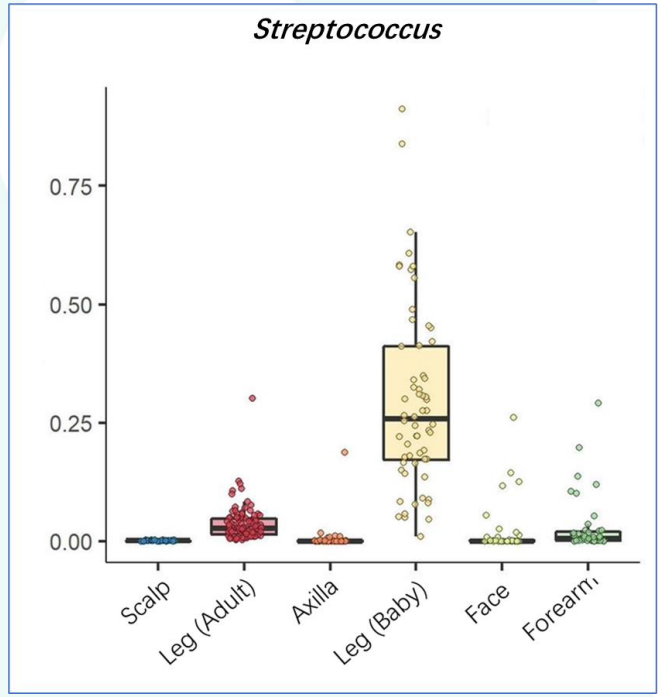


Skin surface lipids drive diversity reduction and the concomitant shift to a microbiota dominated by Cutibacteria

Body Sites – Community Composition





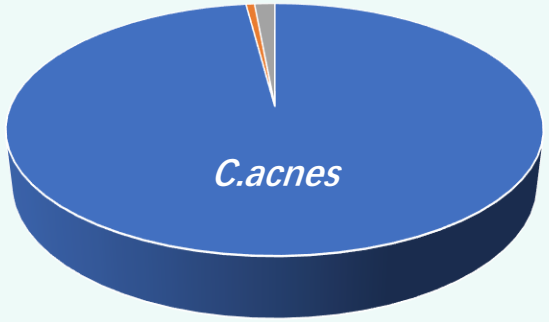


% MRA
331 subjects

Major community commensals with high abundance and prevalence across all sites

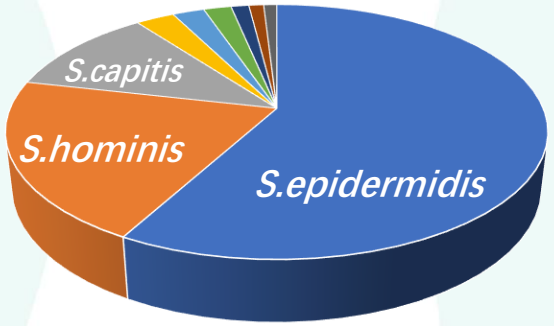
Body Sites – Community Composition

Cutibacterium



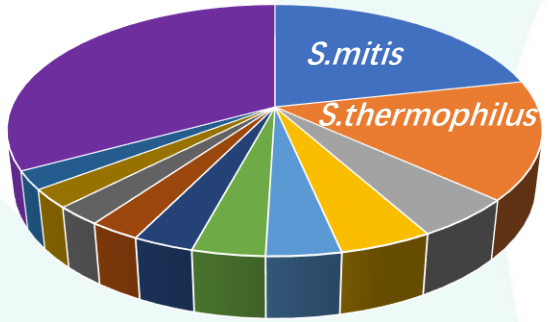
C.acnes *C.avidum* *C.granulosum*

Staphylococcus



S.epidermidis *S.hominis* *S.capitis* *S.haemolyticus* *S.pasteuri|warneri* *S.lugdunensis* *S.aprophyticus* *S.aureus* *Staph_other*

Streptococci



S.mitis *S.thermophilus* *S.salivarius* *S.cristatus* *S.agalactiae* *S.peroris* *S.parasanguinis* *S.dentisani* *S.infantis* *S.infantarius* *S.sanguinis* *S._OTHER*

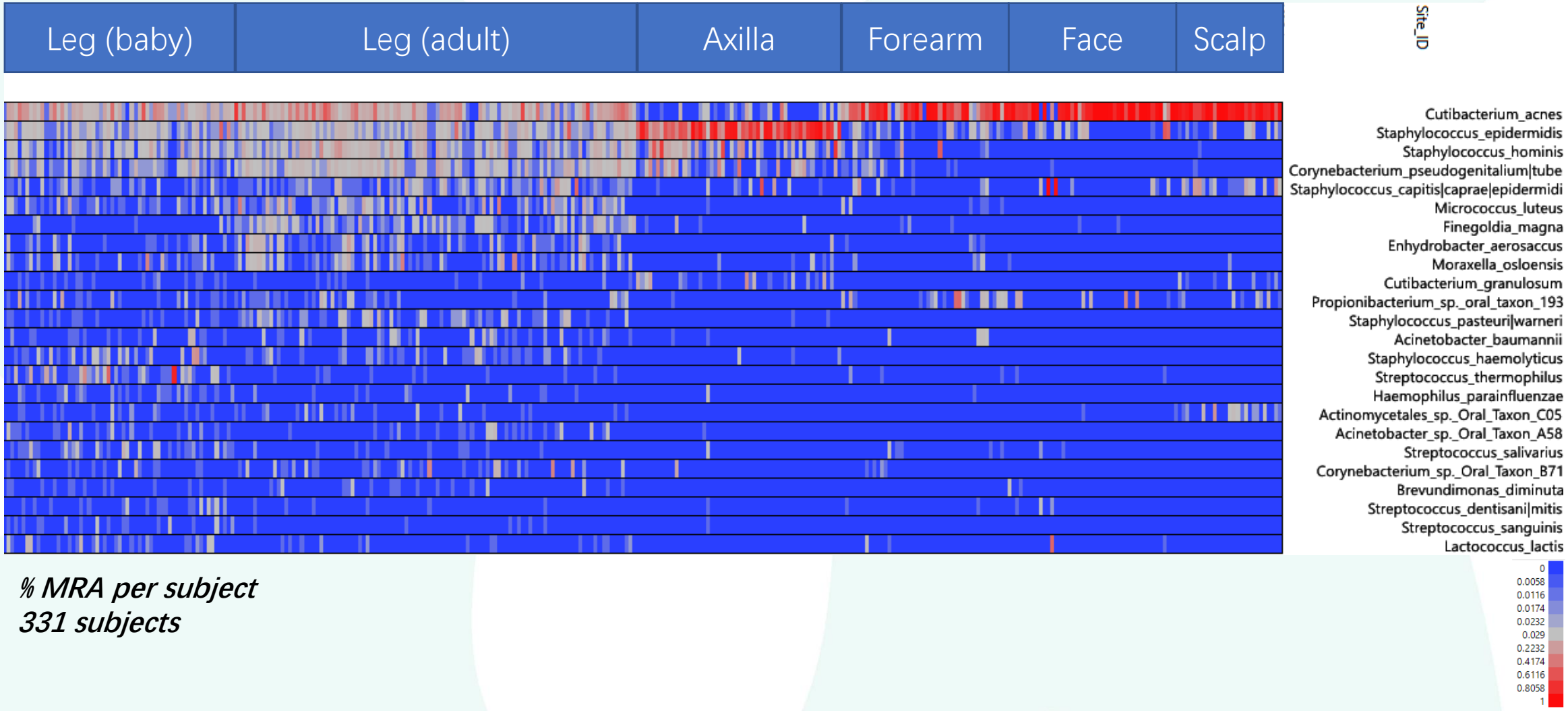
Body Site	C.acnes	C.avidum	C.granulosum
Scalp	99%	0%	1%
Face	100%	0%	0%
Forearm	100%	0%	0%
Adultleg	99%	0%	1%
Babyleg	98%	0%	2%
Axilla	43%	21%	36%

Body Site	S.epidermidis	S.hominis	S.capitis	S.haemolyticus	S.pasteuri|warneri	S.lugdunensis	S.aprophyticus| sp_	S.aureus	Staph_other
Adultleg	30%	35%	15%	4%	8%	0%	5%	1%	3%
Axilla	79%	14%	3%	0%	0%	3%	0%	0%	0%
Babyleg	39%	26%	7%	16%	3%	0%	1%	6%	2%
Face	46%	0%	53%	0%	0%	0%	0%	1%	0%
Forearm	36%	42%	18%	0%	1%	0%	0%	4%	0%
Scalp	28%	1%	71%	0%	0%	0%	0%	0%	0%

Body Site	S.mitis	S.thermophilus	S.salivarius	S.cristatus	S.agalactiae	S.peroris	S.parasanguinis	S.dentisani	S.infantis	S.infantarius	S.sanguinis	S._OTHER
Adultleg	13%	8%	7%	2%	2%	0%	5%	5%	4%	1%	5%	49%
Axilla	3%	0%	22%	6%	0%	0%	10%	4%	9%	1%	4%	40%
Babyleg	26%	20%	5%	6%	0%	5%	3%	2%	2%	3%	2%	35%
Face	39%	5%	6%	0%	13%	0%	1%	8%	1%	0%	1%	21%
Forearm	5%	4%	9%	0%	69%	0%	1%	1%	0%	0%	1%	11%
Scalp	31%	11%	1%	2%	1%	0%	2%	16%	6%	0%	4%	34%

Species as % of genera MRA
331 subjects

Body Sites – Community Composition

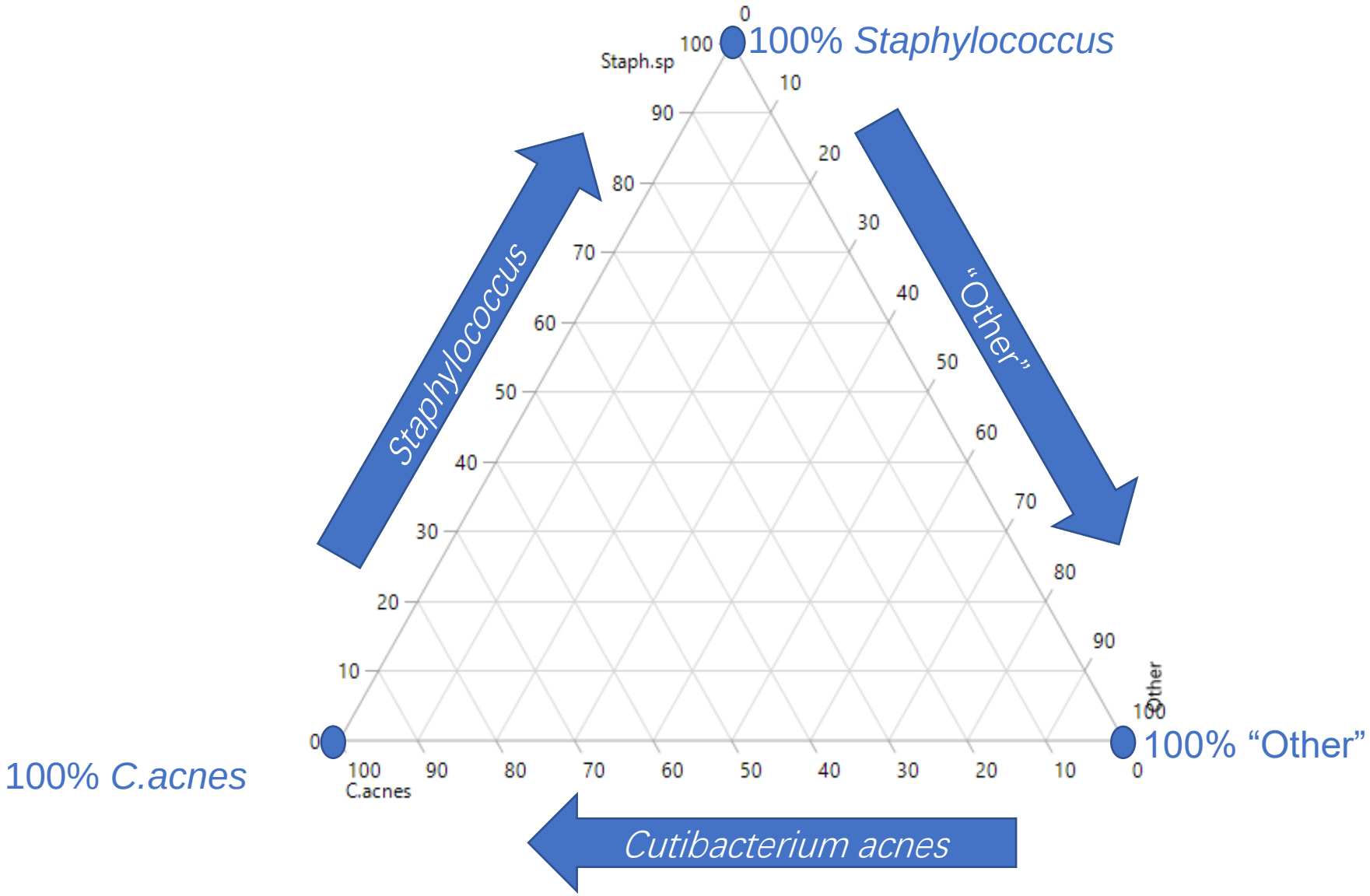


% MRA per subject
331 subjects

Body Site & Environment

Unilever

Body Sites – Community Composition

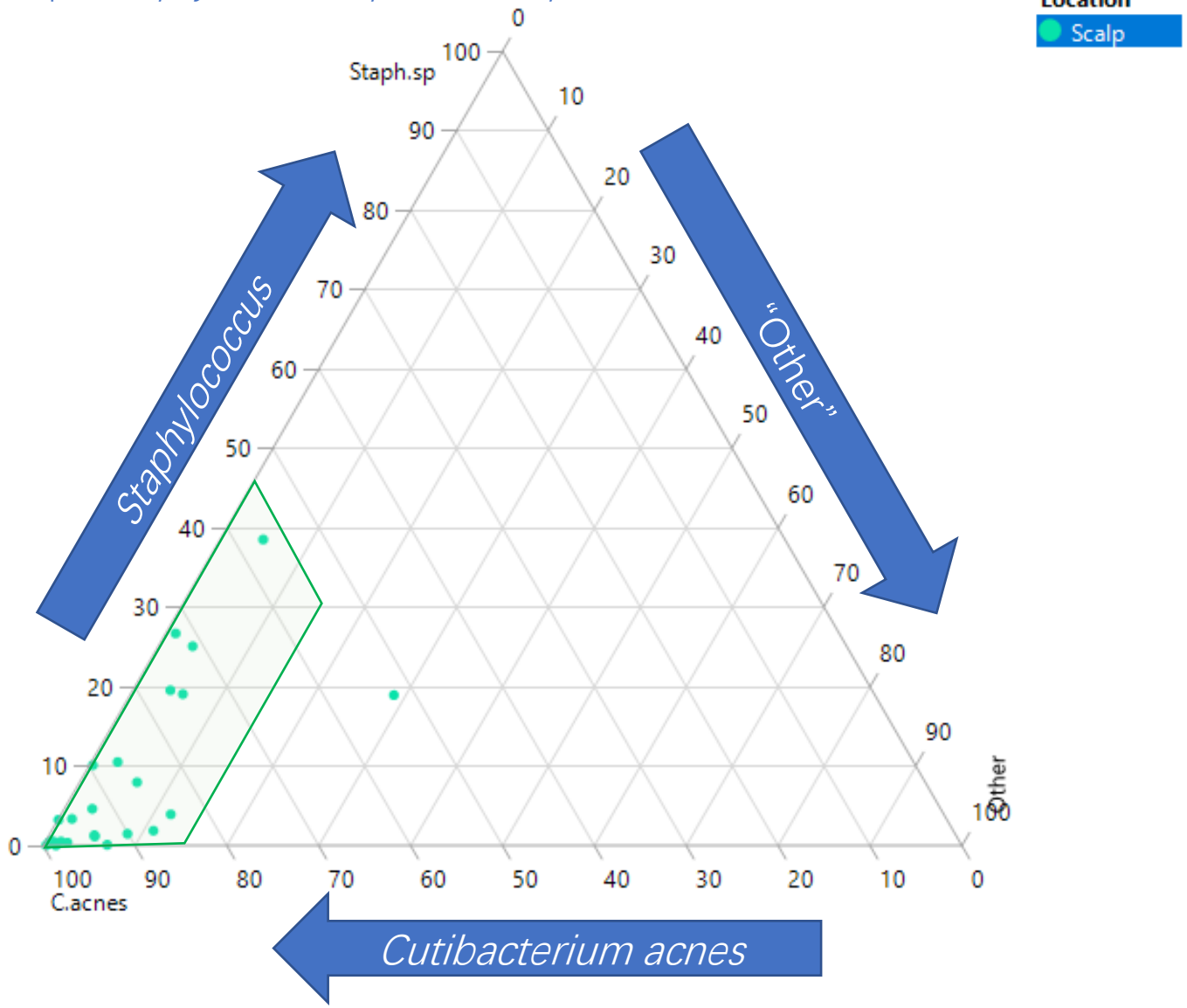


Body Site & Environment

Unilever

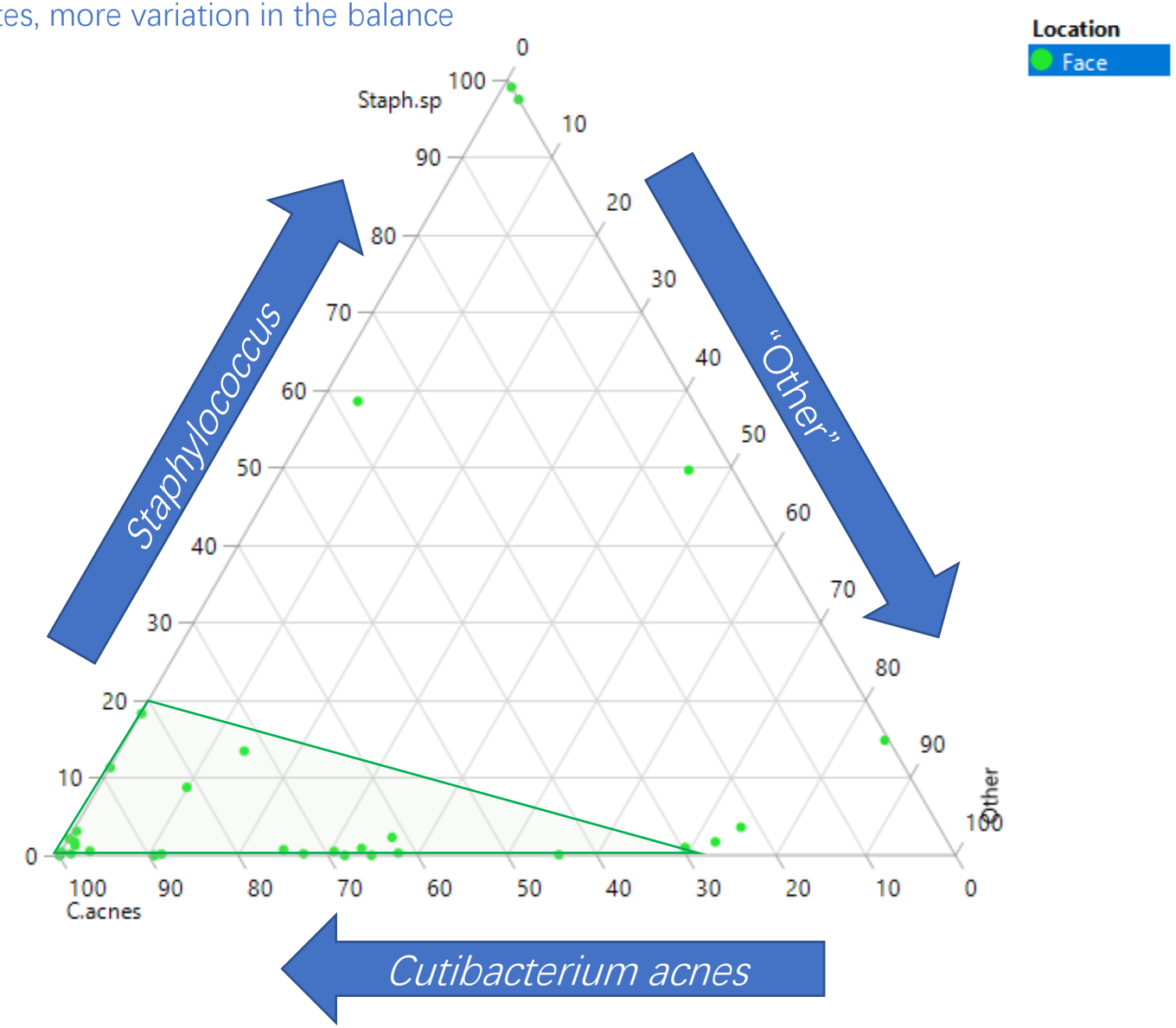
Body Sites – Community Composition

Scalp: *Cutibacterium* dominates, plus *Staphylococcus capitis* and *S. epidermidis*



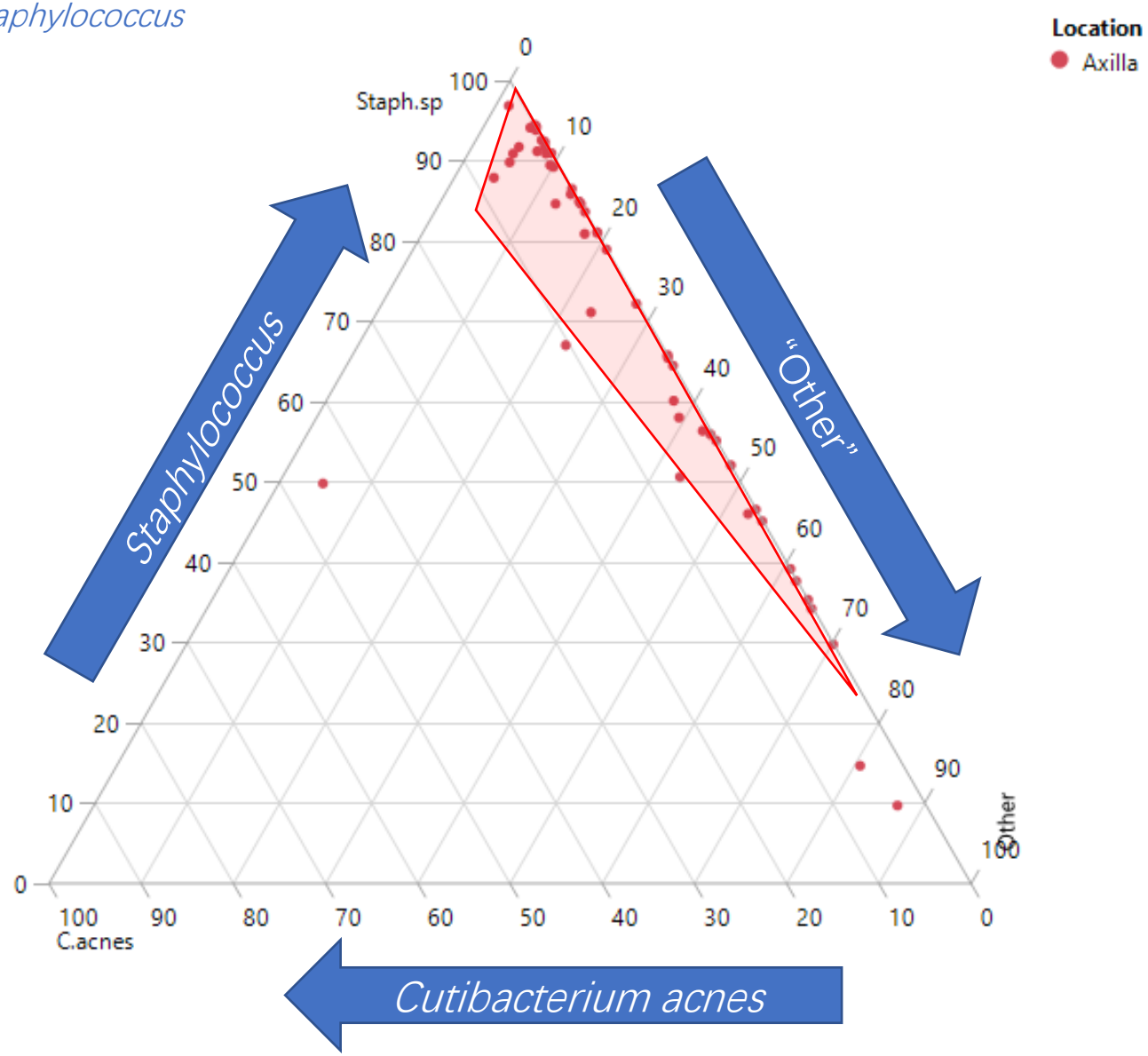
Body Sites – Community Composition

Face: *Cutibacterium* dominates, more variation in the balance



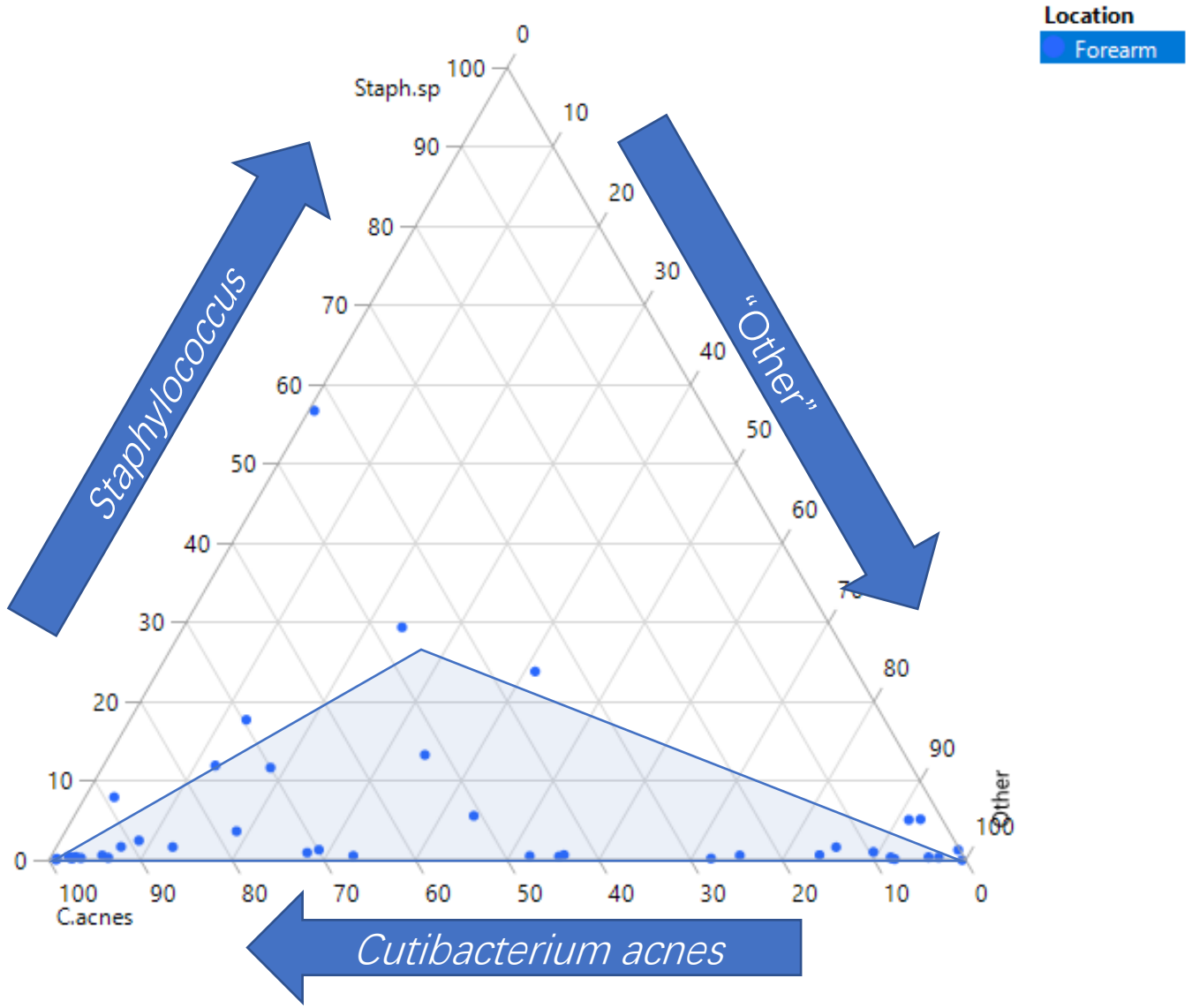
Body Sites – Community Composition

Axilla: High dominance of *Staphylococcus*



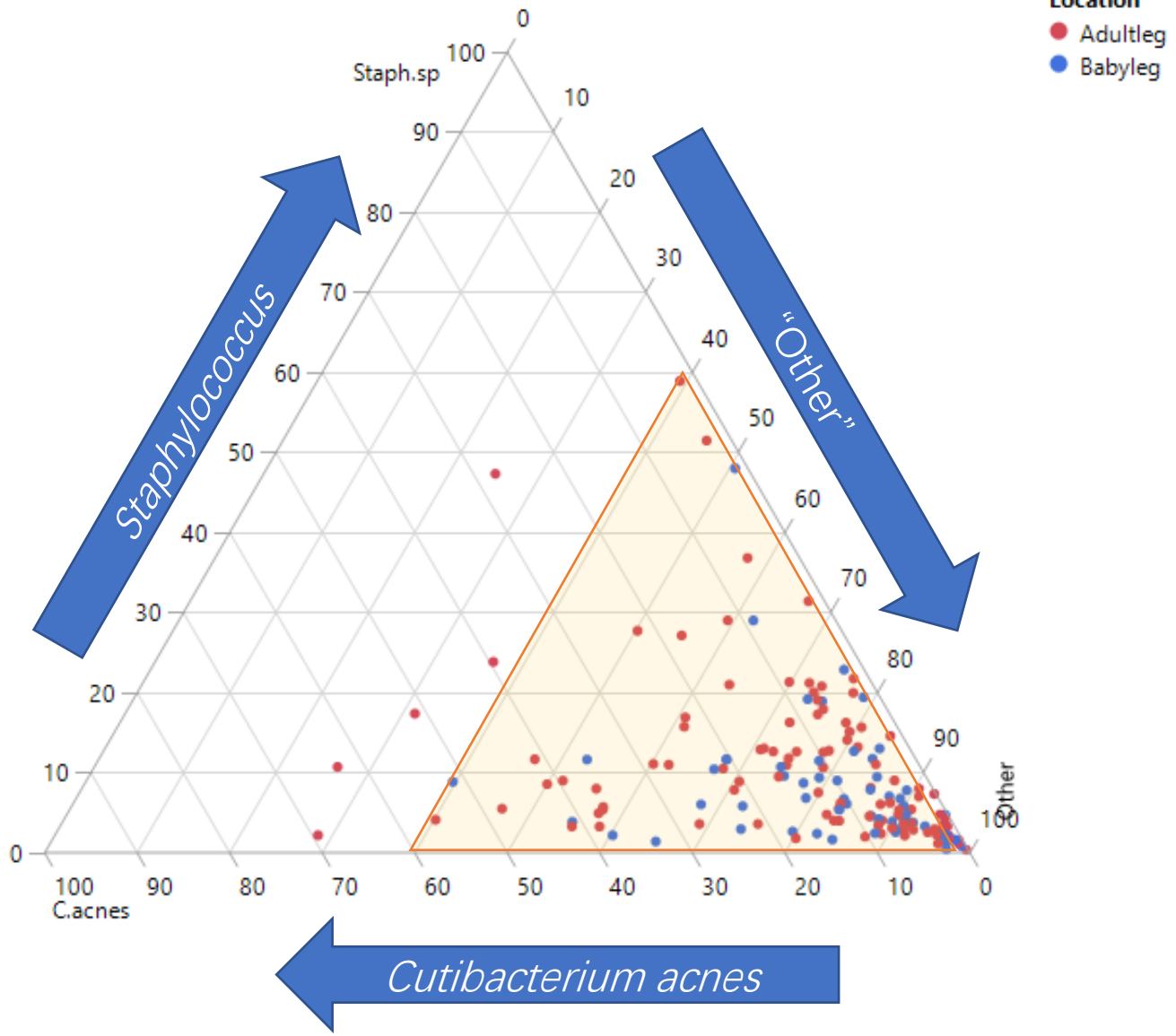
Body Sites – Community Composition

Arm: Although well represented, Cuti and Staphs are less dominant



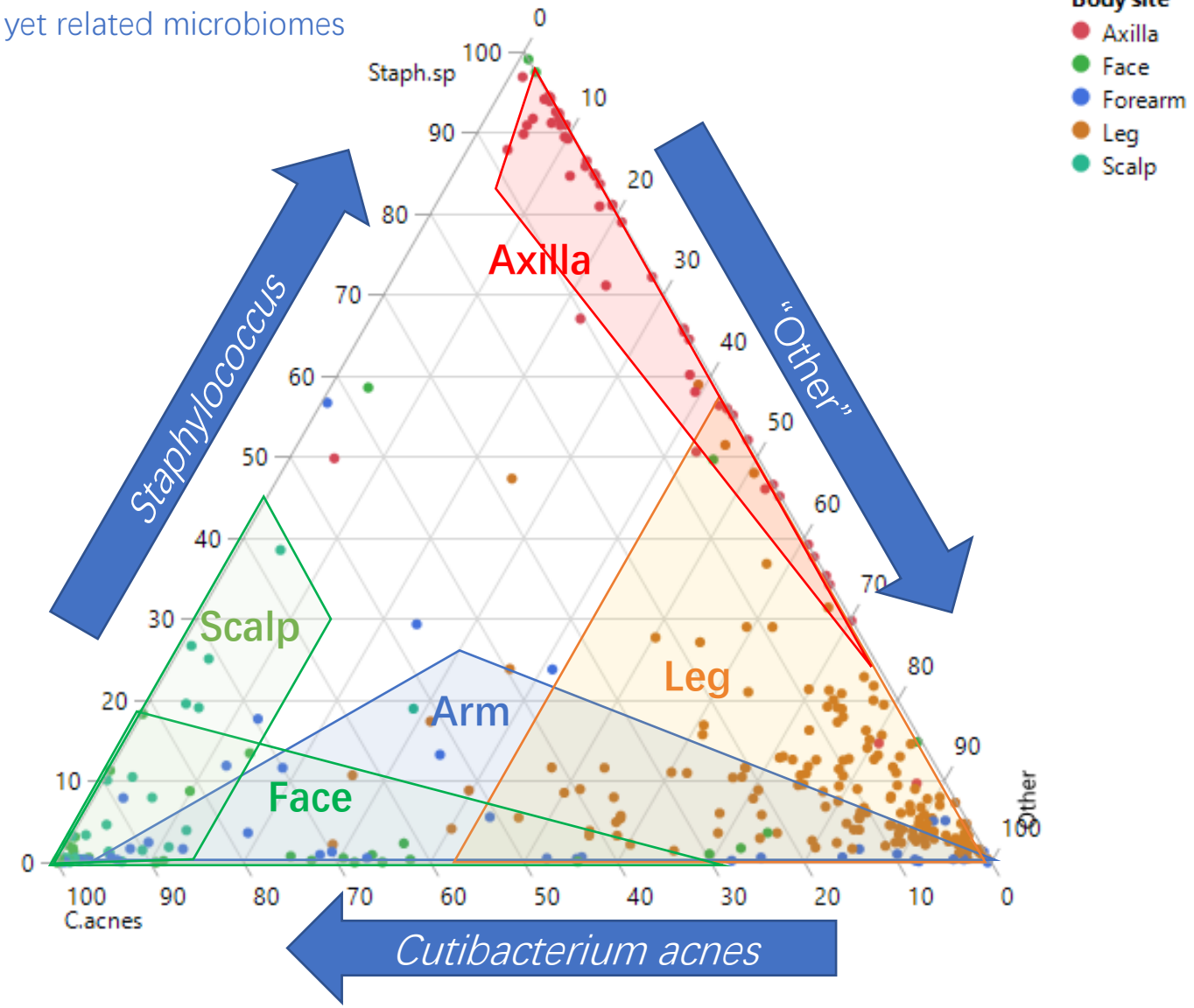
Body Sites – Community Composition

Leg: Cuti and Staphs still significant but dialled back somewhat Vs. Arm



Body Sites – Community Composition

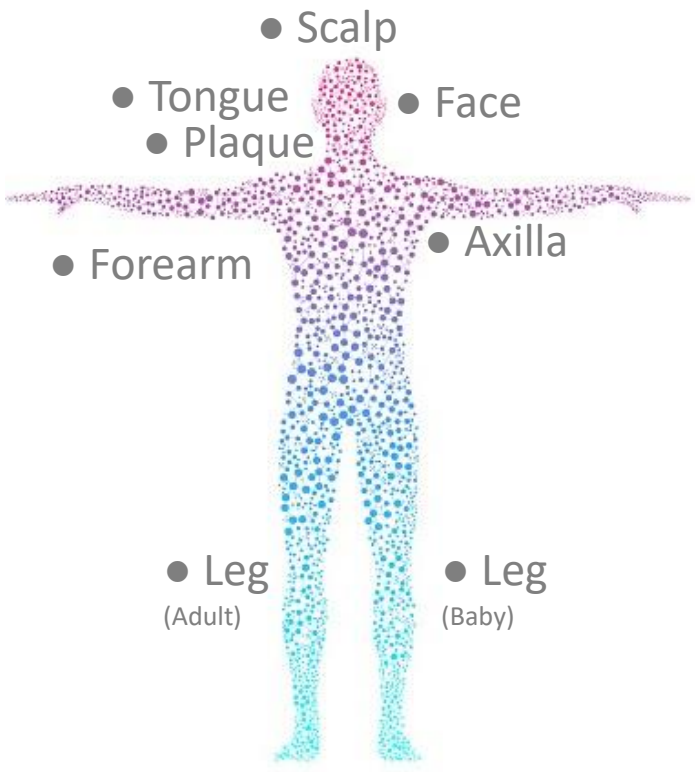
Variations on a theme
Body site niches have distinct yet related microbiomes



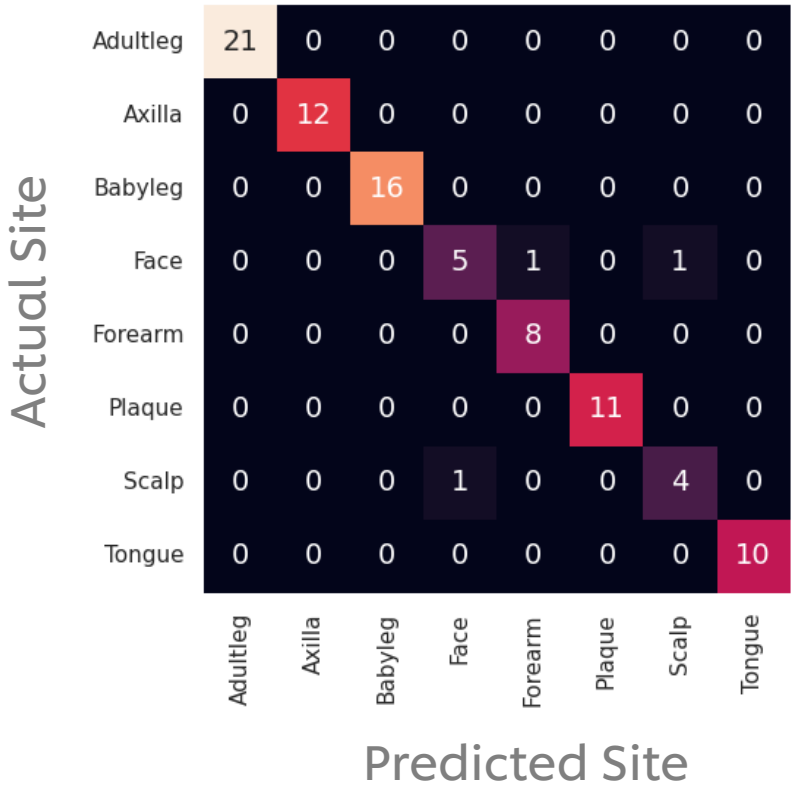
AI Prediction

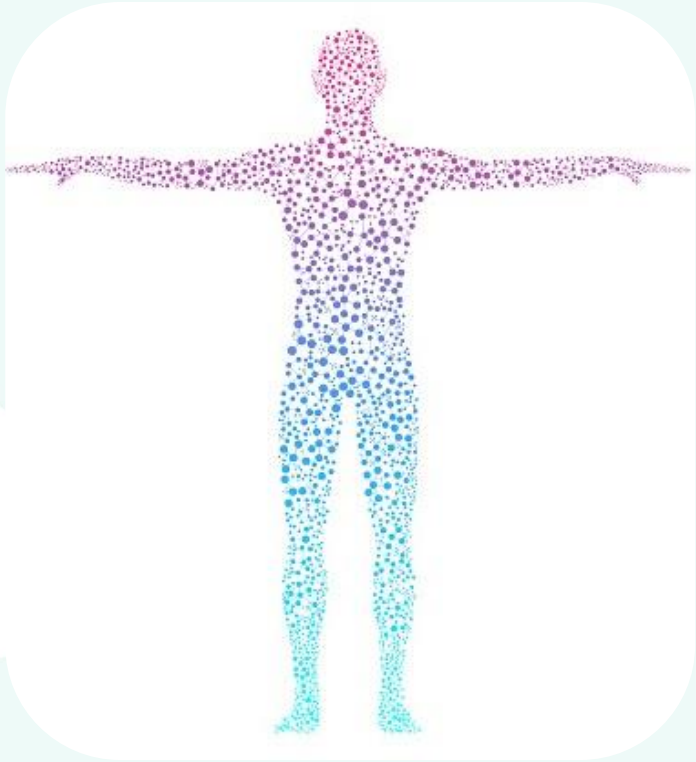
Body Site & Environment

450 Samples



A.I. Accuracy = 93%
(validation data)

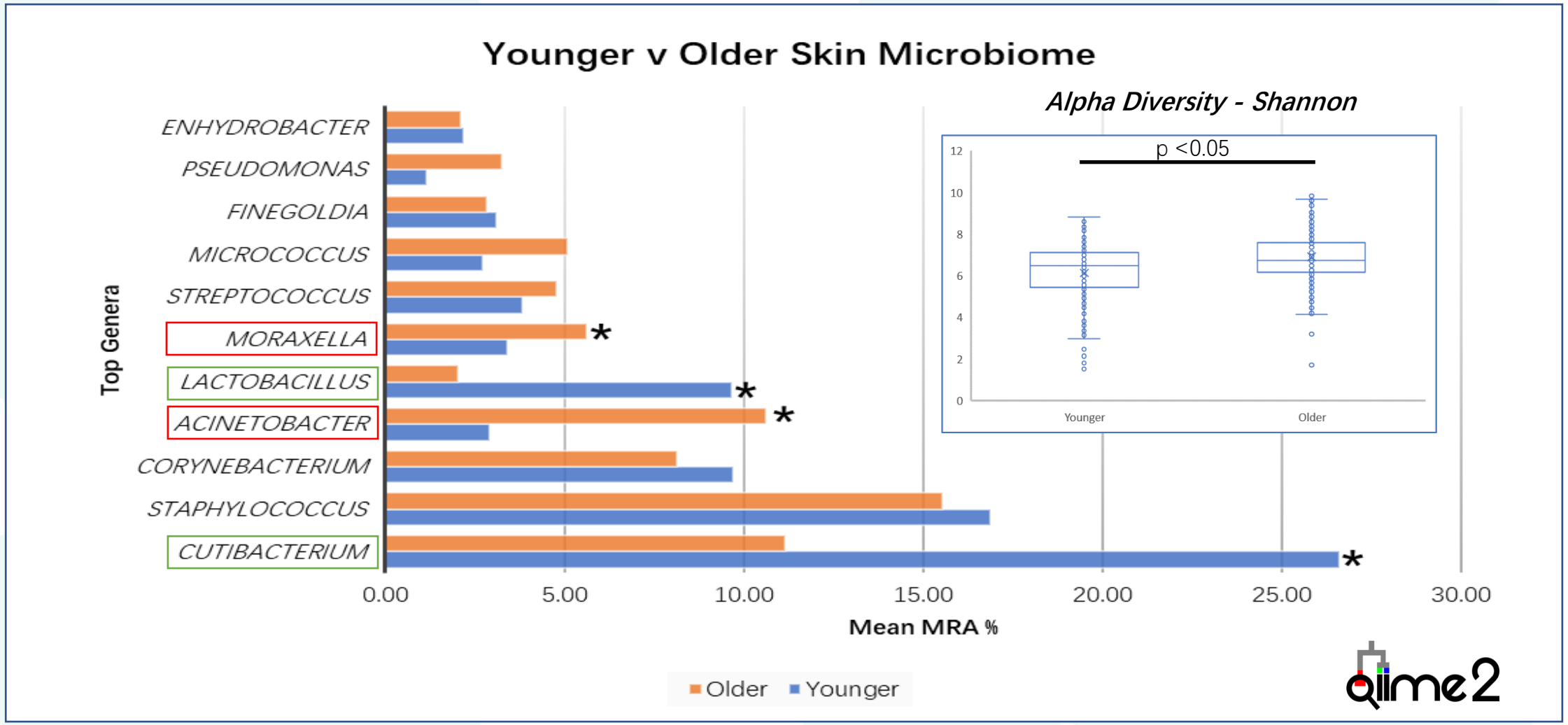




Age

Microbiome changes

Older = 50-55 (268 samples)
Younger = 21-41 (273 samples)



Younger skin:

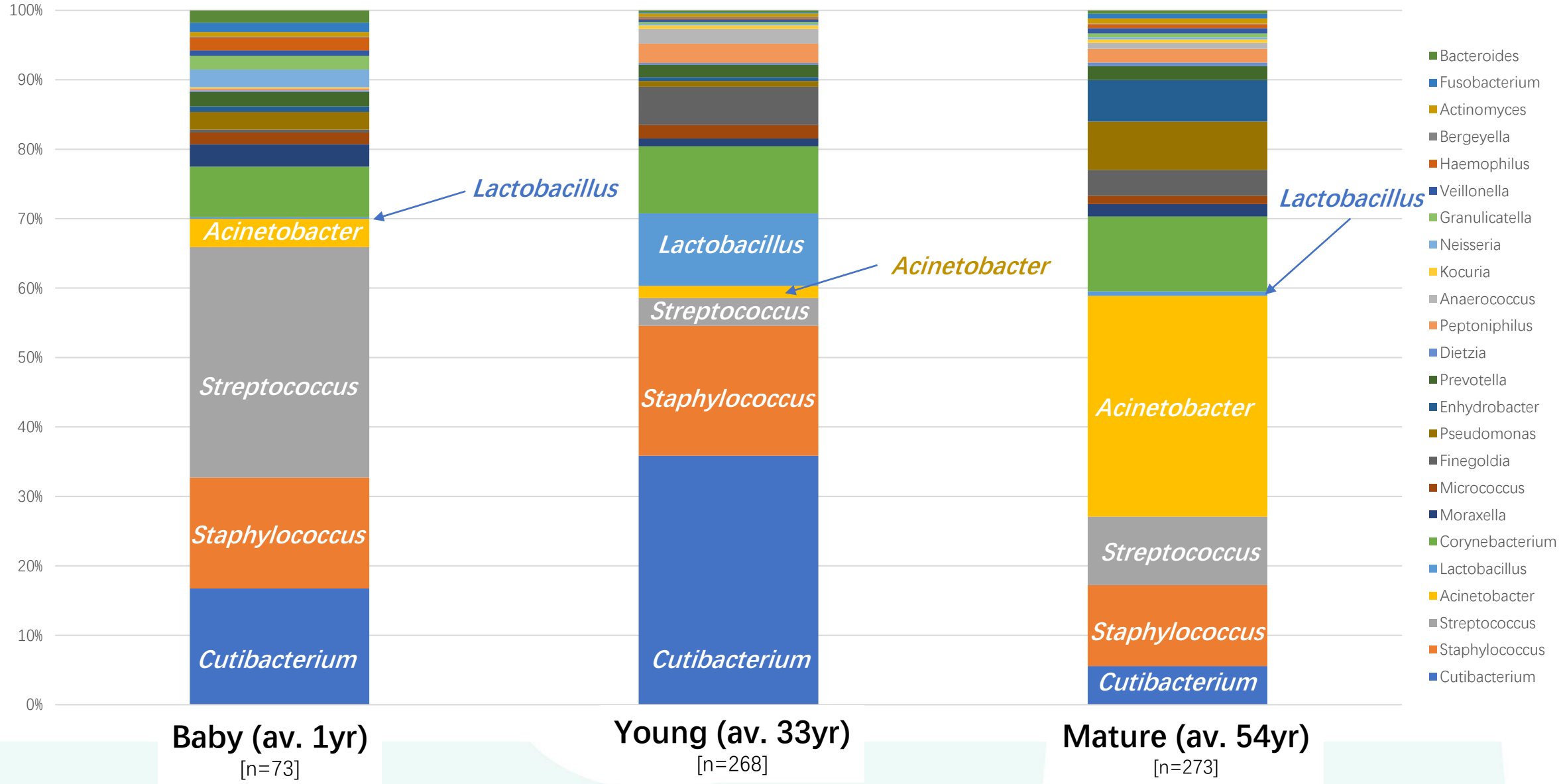
- Higher abundance of *Cutibacterium and Lactobacillus*

Older Skin

- Higher Abundance of *Acinetobacter* and *Moraxella*

Microbiome changes with age

Age & Microbiome



Baby (av. 1yr)
[n=73]

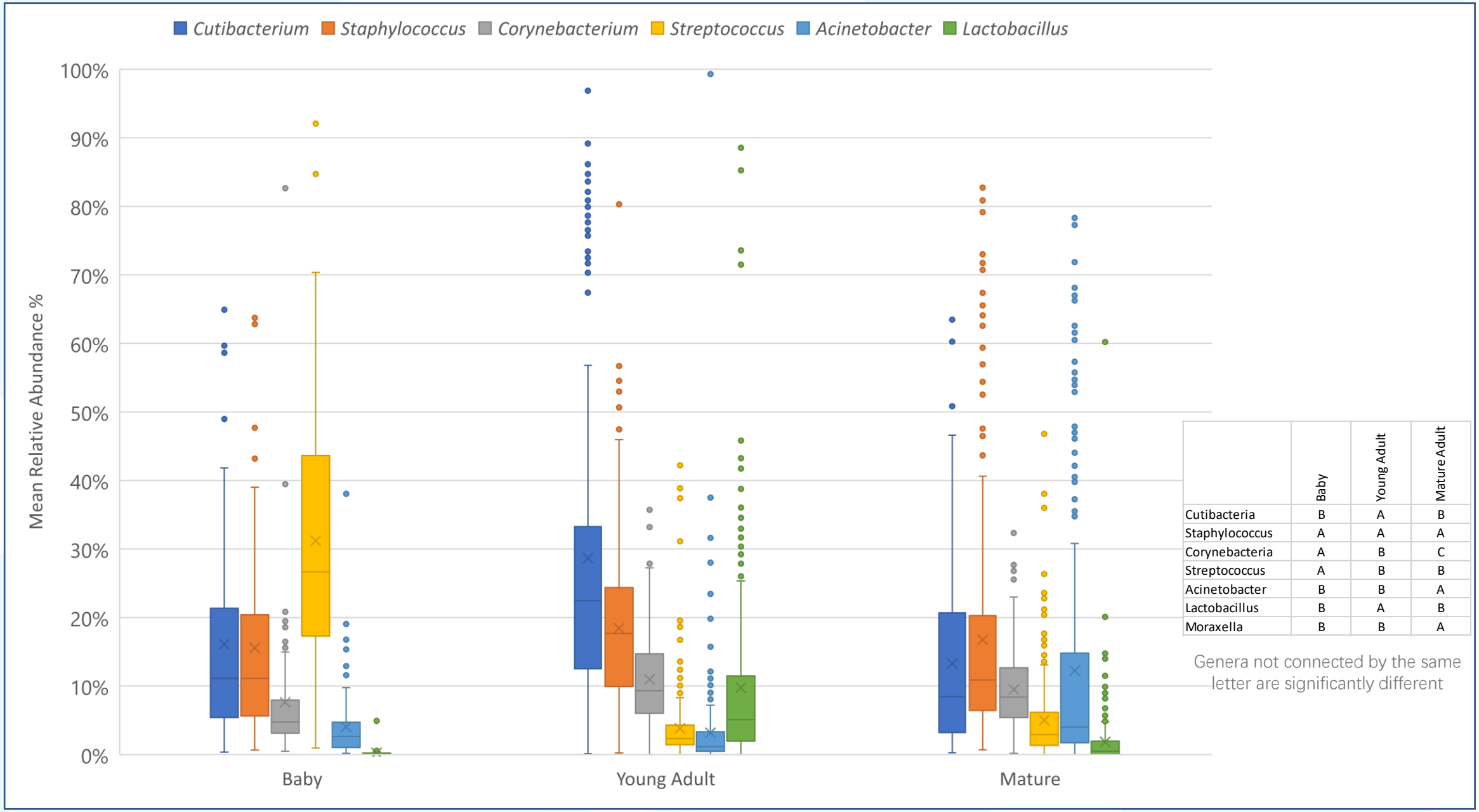
Young (av. 33yr)
[n=268]

Mature (av. 54yr)
[n=273]

Unilever

Microbiome changes with age

Age & Microbiome

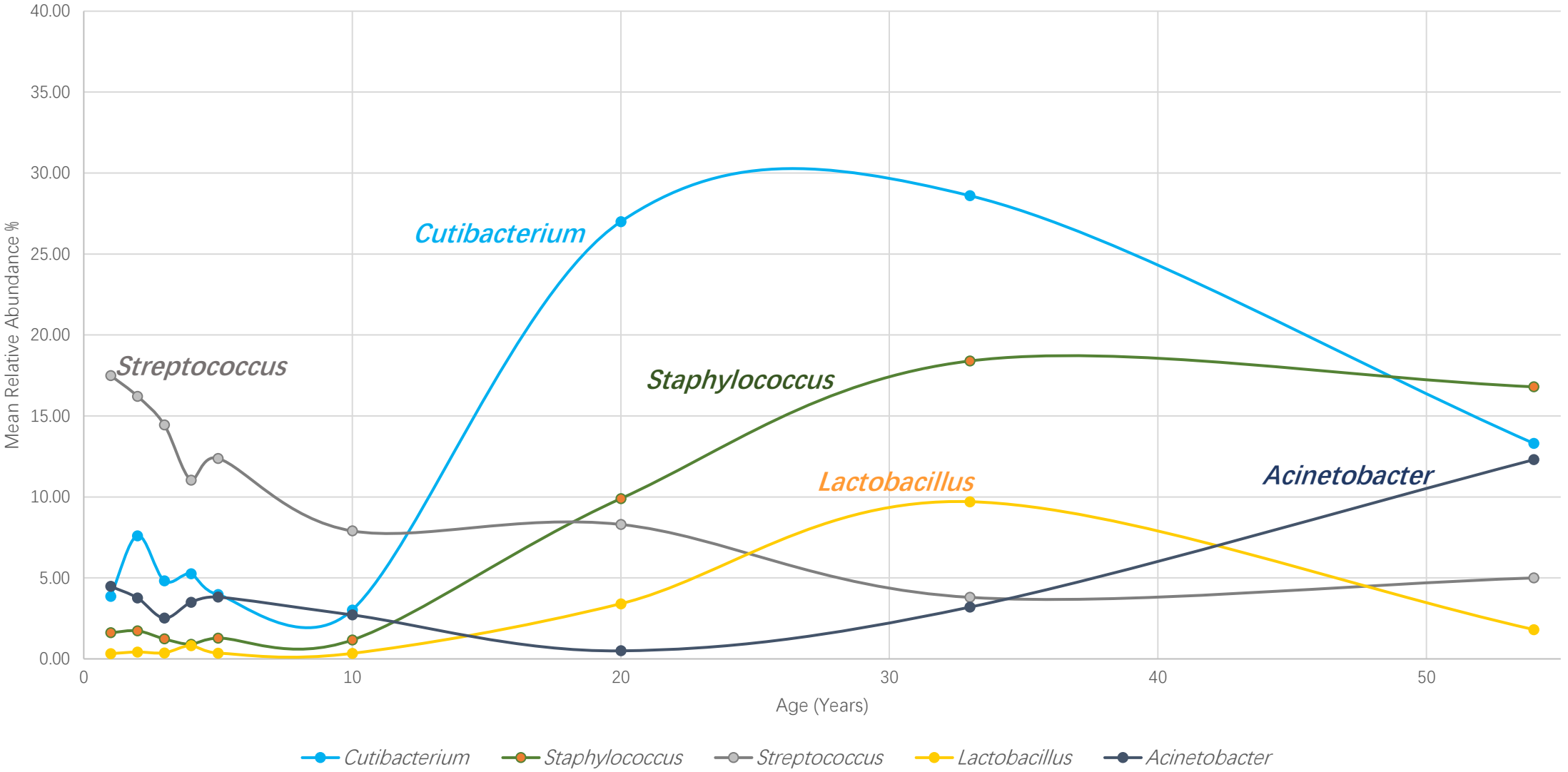


	Baby	Young Adult	Mature Adult
Cutibacteria	B	A	B
Staphylococcus	A	A	A
Corynebacteria	A	B	C
Streptococcus	A	B	B
Acinetobacter	B	B	A
Lactobacillus	B	A	B
Moraxella	B	B	A

Genera not connected by the same letter are significantly different

Skin Microbiome: Through the Years

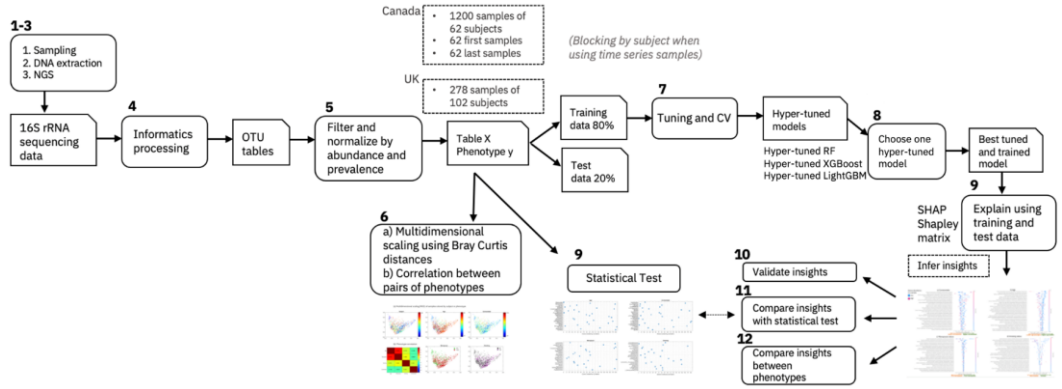
Age & Microbiome

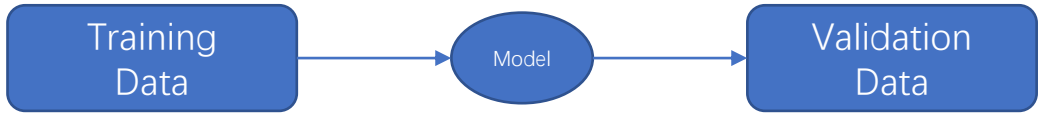


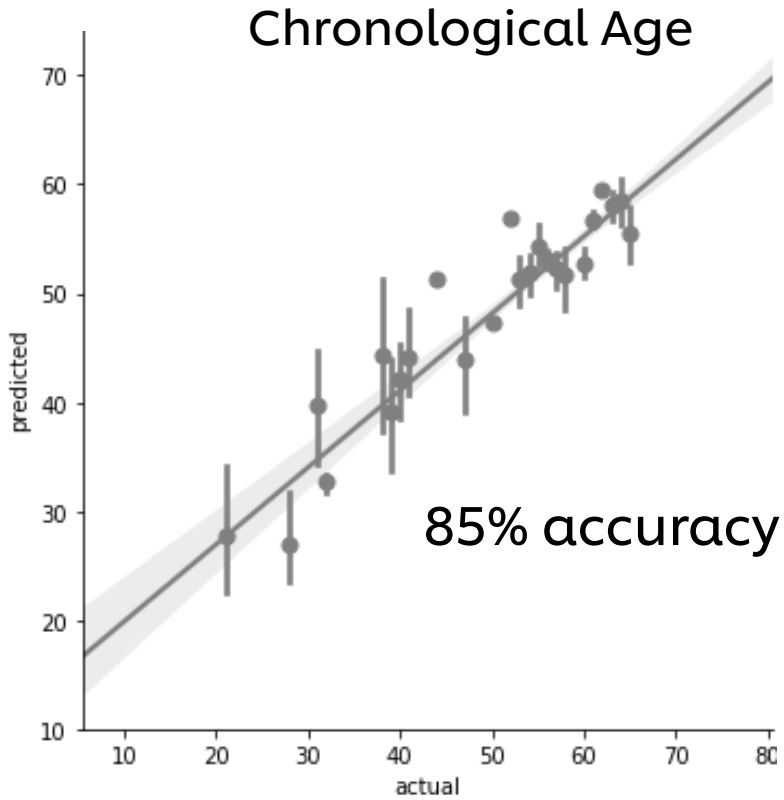
Capone et al., 2011, Shibagaki et al 2017, Zhu et al., 2019, Carrieri et al., 2021, Howard et al 2021, Park et al., 2022

Prediction

Accurate predictions of age from microbiome







Subject Metadata Prediction Accuracies:
Age: 85% Hydration: 90% Smoking Status: 85% Pre/Post Menopause: 92%

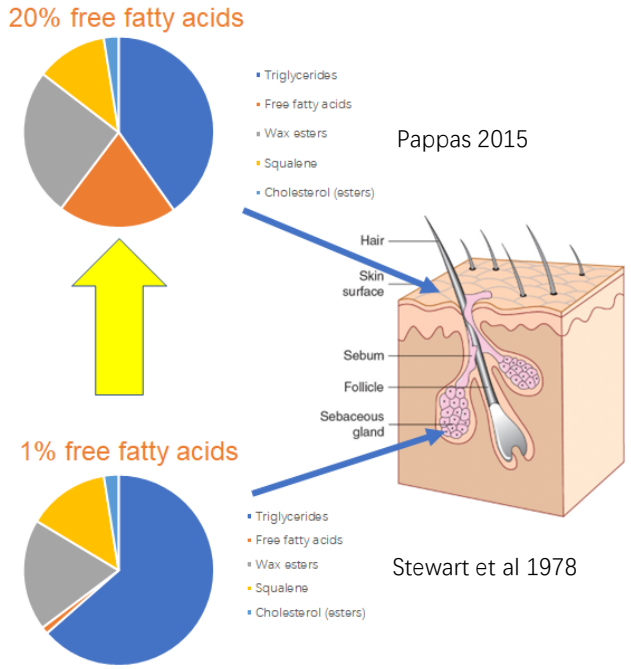
Carrieri, A.P., Haiminen, N., Maudsley-Barton, S. *et al.* Explainable AI reveals changes in skin microbiome composition linked to phenotypic differences. *Sci Rep* **11,** 4565 (2021). https://doi.org/10.1038/s41598-021-83922-6

Why does it matter?

Cutibacterium acnes & Skin surface lipids

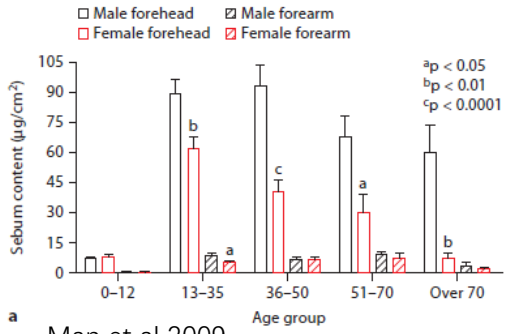
Cutibacterium

Sebaceous lipids



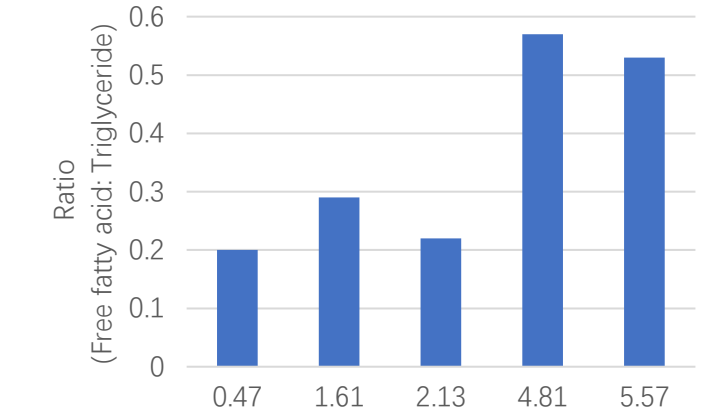
Pappas 2015

Stewart et al 1978

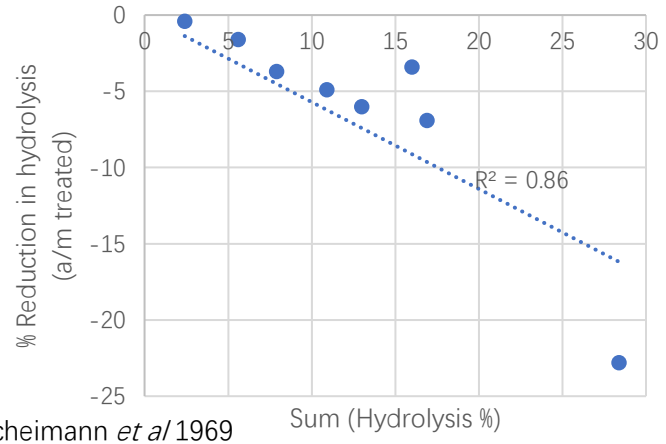


Man et al 2009

Microbial Hydrolysis

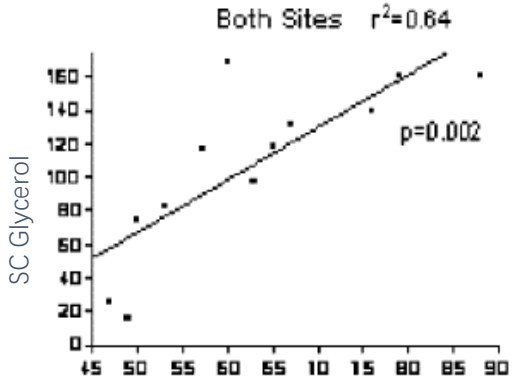


McGinley *et al* 1980

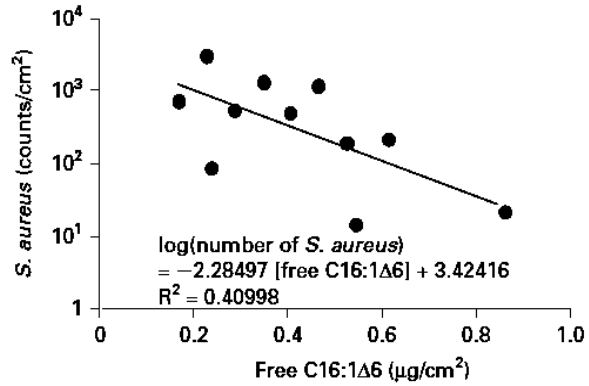


Scheimann *et al* 1969

Effects on Skin



Elias *et al* 2005

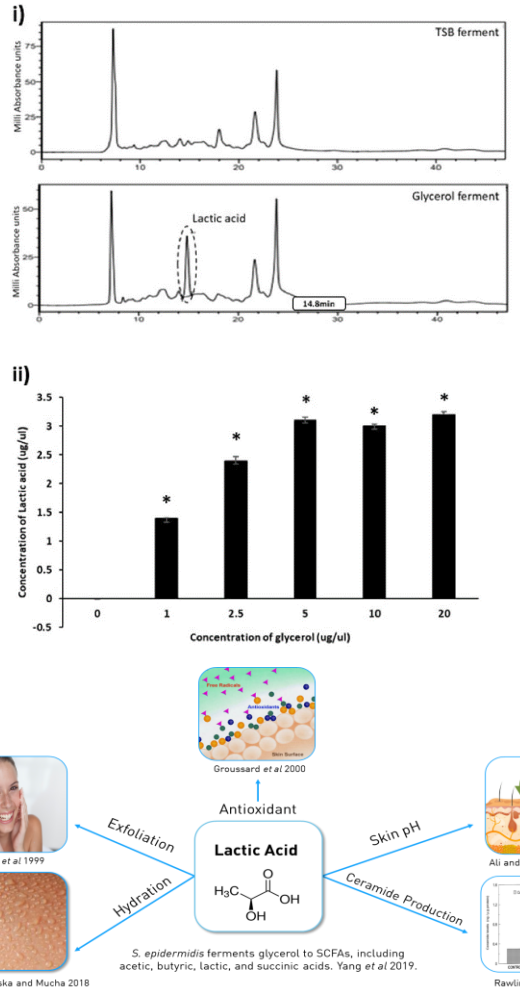


Takigawa *et al* 2005

Staphylococcus epidermidis

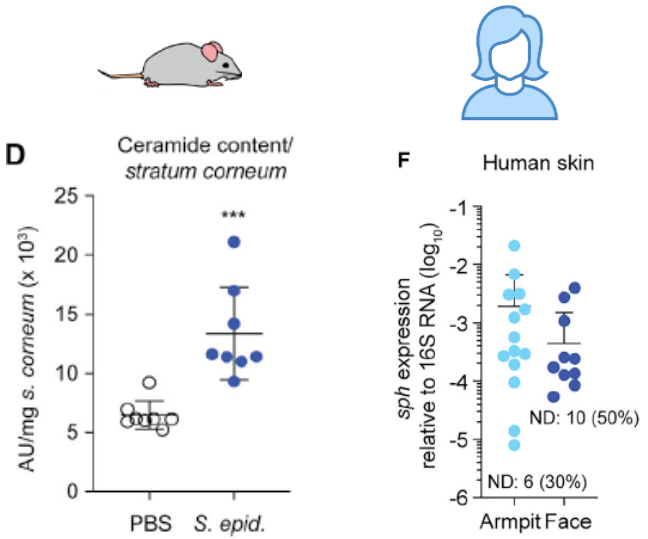
Staphylococci

Lactic acid



Salgaonkar et al 2021

Barrier & Sphingomyelinase

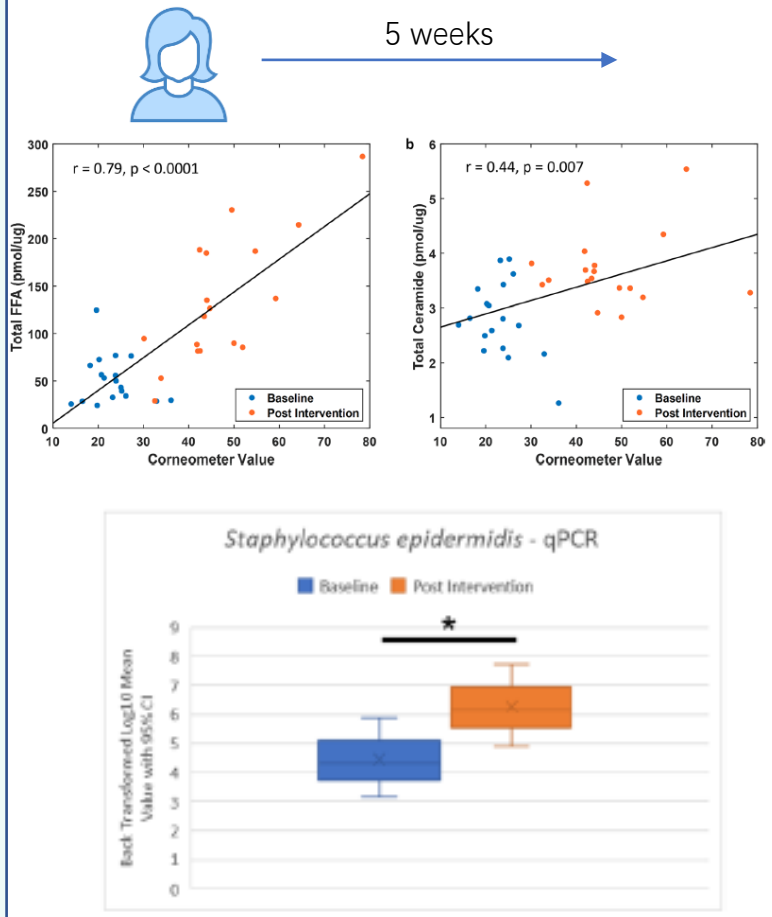


Highlights

- Commensal *Staphylococcus epidermidis* contributes to skin barrier homeostasis
- *S. epidermidis* produces a sphingomyelinase that helps generate protective ceramides
- Sphingomyelinase contributes to *S. epidermidis* skin colonization
- *S. epidermidis* prevents skin dehydration via its sphingomyelinase activity

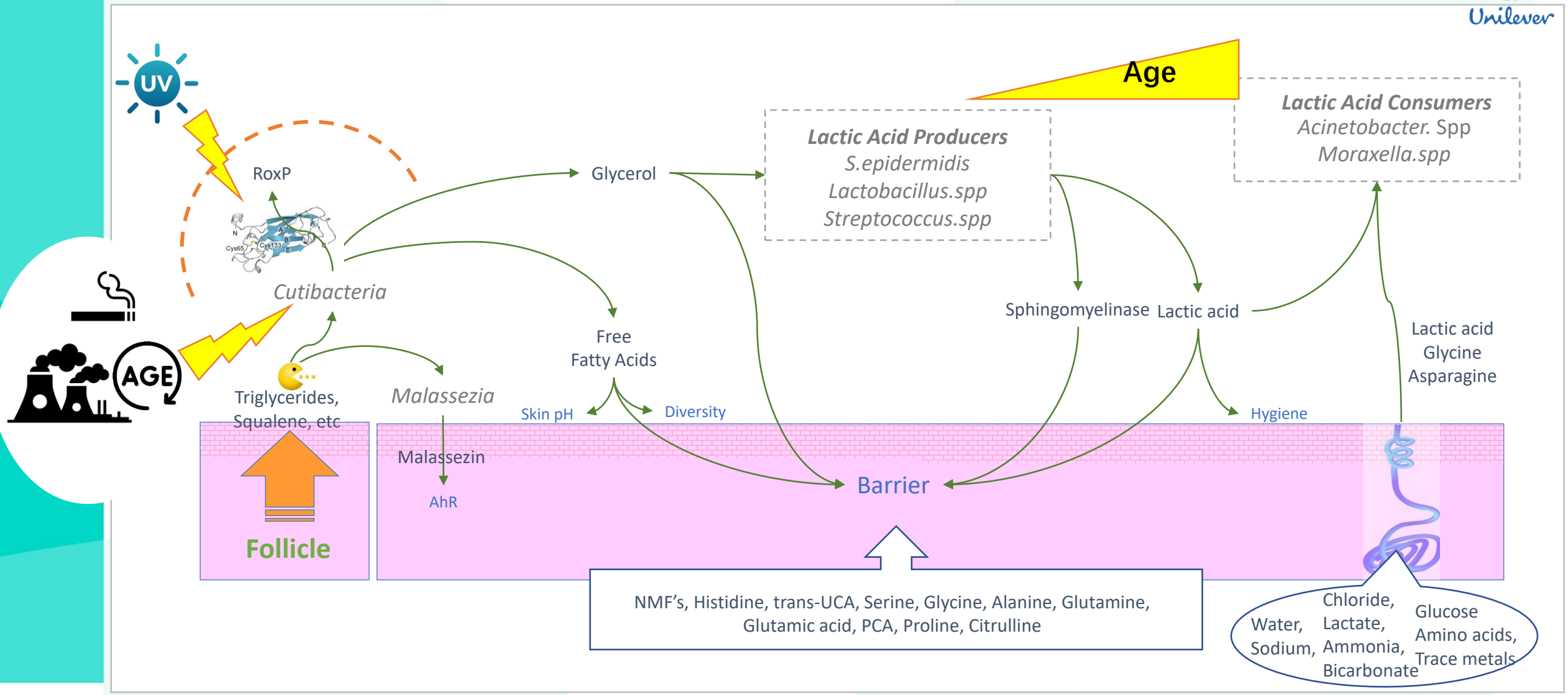
Zheng et al 2022

Topical treatment



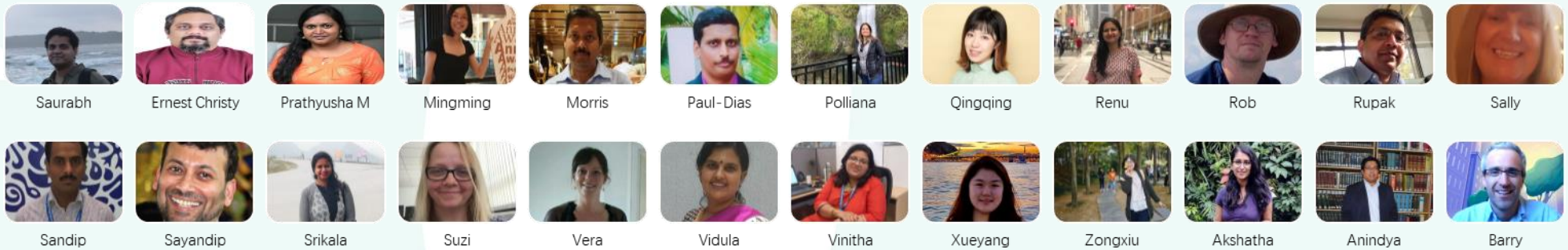
Murphy et al 2022

Bringing it all together



Cutibacteria & skin surface lipids: Nicolaides 1958, Strauss 1966, Kraus 1968, Freinkel 1968, Scheimann 1969, Greene 1970, Marples 1970, Kellum 1973, Nicolaides 1974, Puhvel 1975, Stewart 1978, McGinley 1980, Cove 1980, Downie 1998. **RoxP:** Stødkilde 2022. **Lactic acid bacteria:** Ahle 2022, Zheng 2022, Salgaonkar 2021, Hayashi 2021, Nishioka 2021, Wilson 2008, Marzio 1999. **Eccrine sweat:** Harker & Harding 2013, Baker & Wolfe, 2020. **Malassezia:** Gaitanis et al 2008. **NMF:** Kroll et al 2012

Thanks



Unilever