Primary prevention in atopic dermatitis

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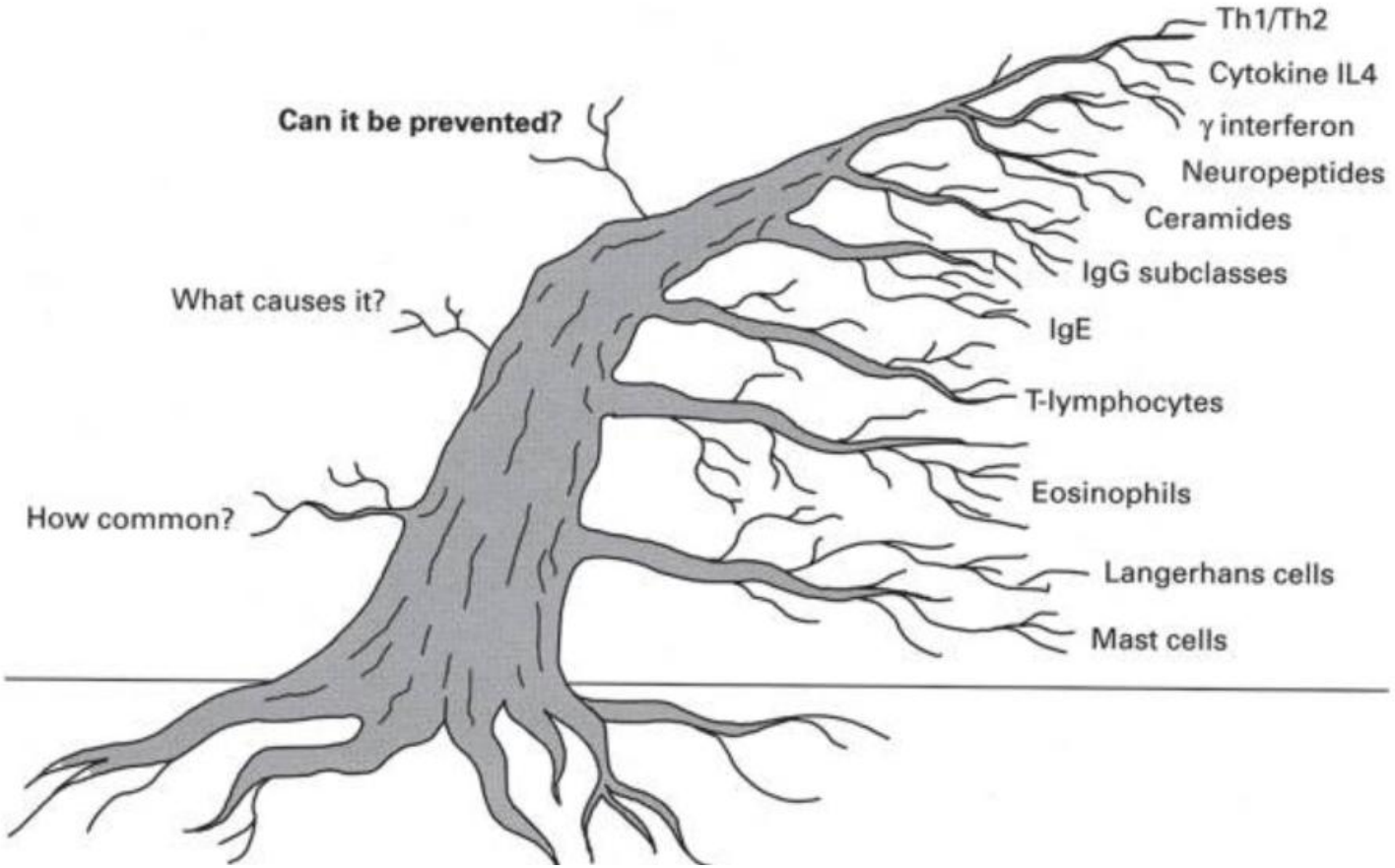
What I will cover

- Principles of primary prevention
- Infections and farm environments
- Probiotics
- Breastfeeding
- Strengthening the skin barrier
- Water hardness



Prevention is better than cure!

Most research focuses on investigating established disease.

Williams, H et al. 2020

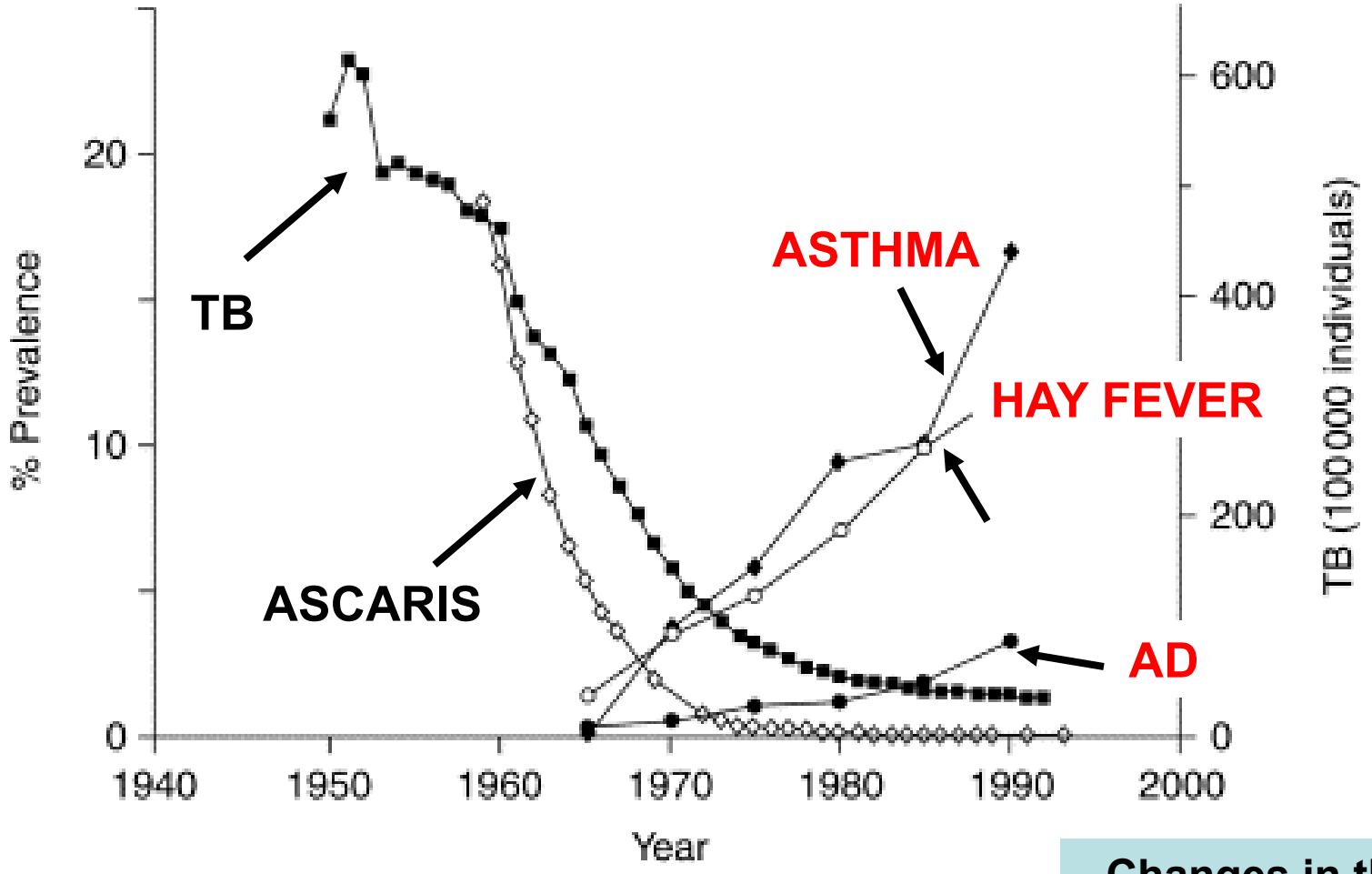
INFECTIONS↑?

The 'hygiene hypothesis'

HAY FEVER/ AD↓

Strachan D. Hay fever, hygiene, and household size. *BMJ* 1989

Infectious diseases↓ allergies↑
Ecological observation



Changes in the prevalence of infectious and allergic diseases
Japanese pre-school examination

A matter of balance?

Parasites↑

Allergies/AD↓

The helminth paradox

ACUTE

hypersensitivity reaction

–

\+

IL-4, IL-5, IL-13 ↑

IgE ↑ and eosinophilia

\+

\+

T cell apoptosis

Prevention of mast cell degranulation

Anti-inflammatory cytokines↑

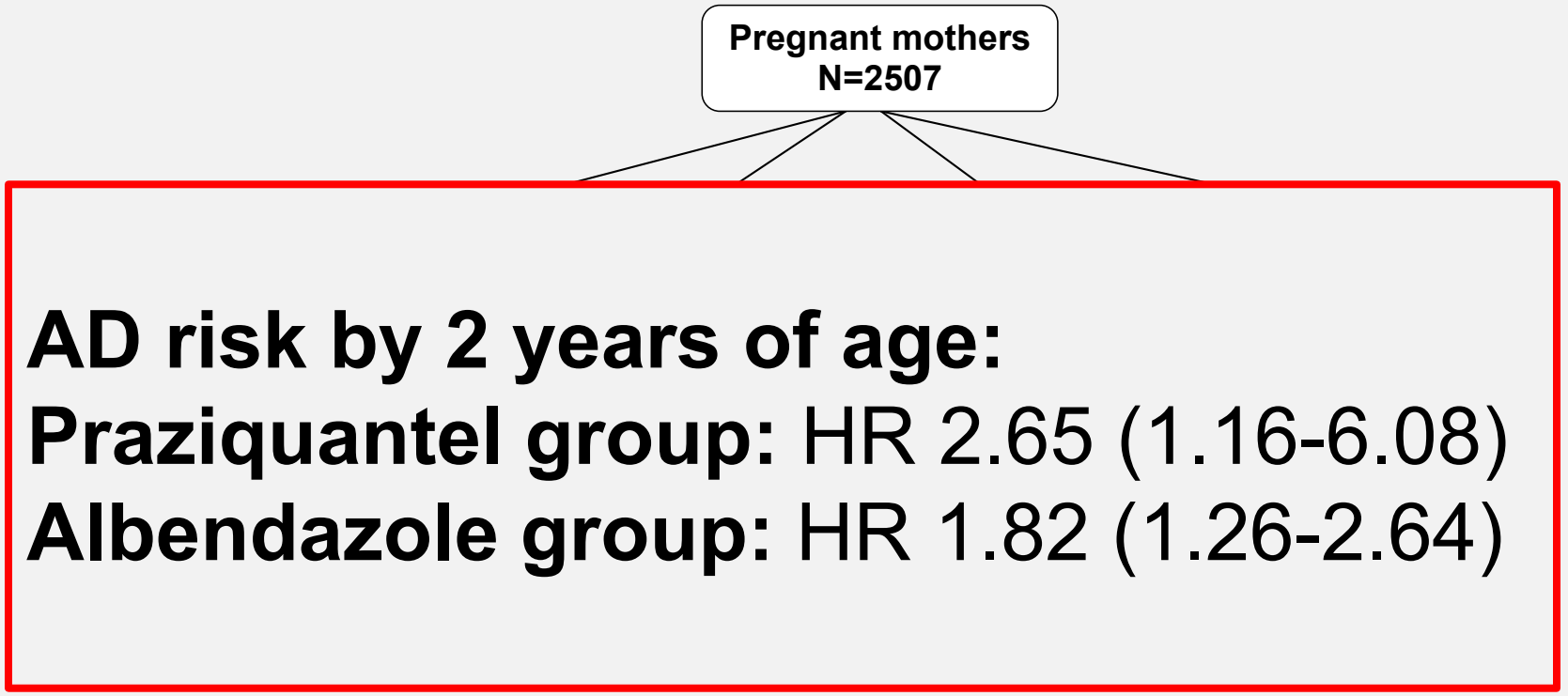
–

Atopy & Allergic disease

CHRONIC

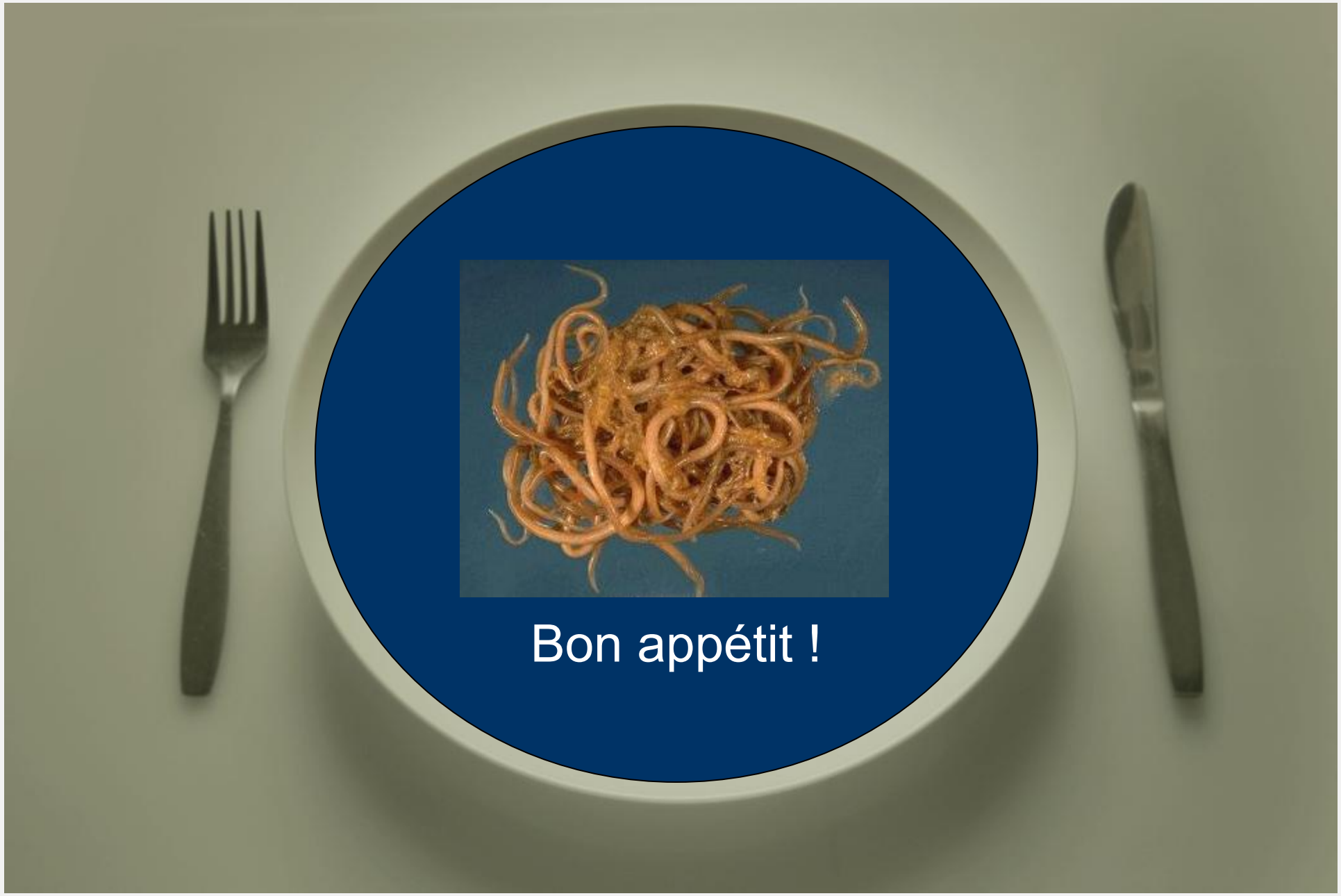
Flohr et al. CEA 2009

Ugandan RCT
pregnant mothers & babies



Hookworm >40%
***Schistosoma mansoni* ~20%**

Mpairwe & Elliott 2010


Bon appétit !


DIRECT EXPOSURE TO FARM ANIMALS DURING PREGNANCY PROTECTS AGAINST AD AND ALLERGIES
FACTORS NOT FULLY UNDERSTOOD (MORE THAN JUST THE MICROBIOME)

CONTACT WITH FARM ANIMALS IN EARLY LIFE ALSO REDUCES THE RISK OF AD

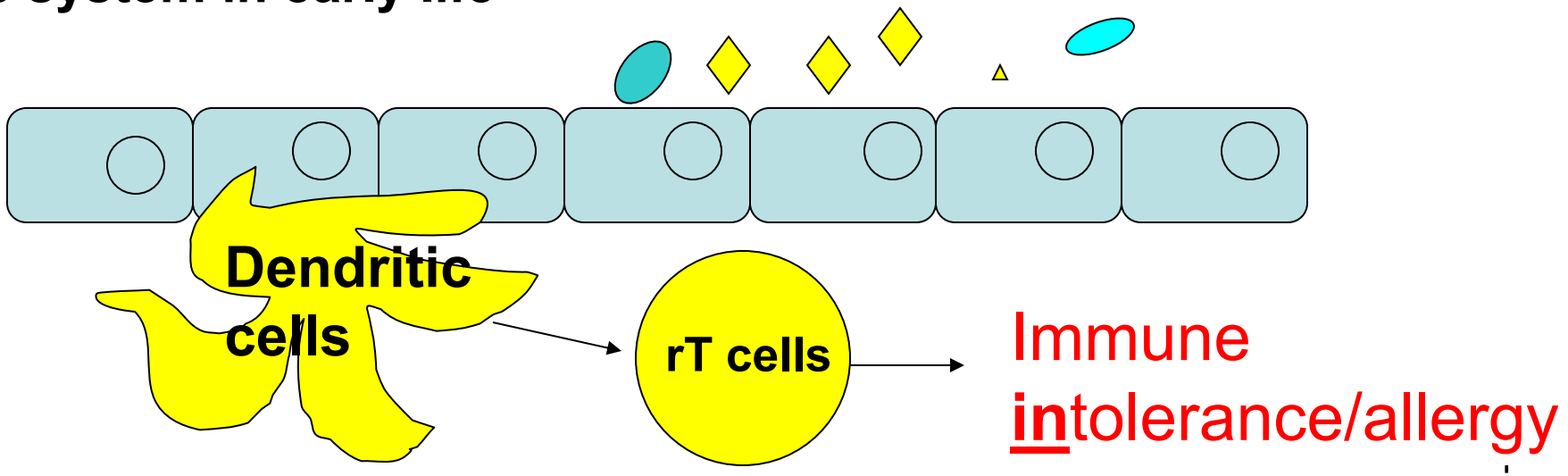
gut parasites ↓

farm environment (pregnancy) ↓

unpasteurised farm milk (child) ↓

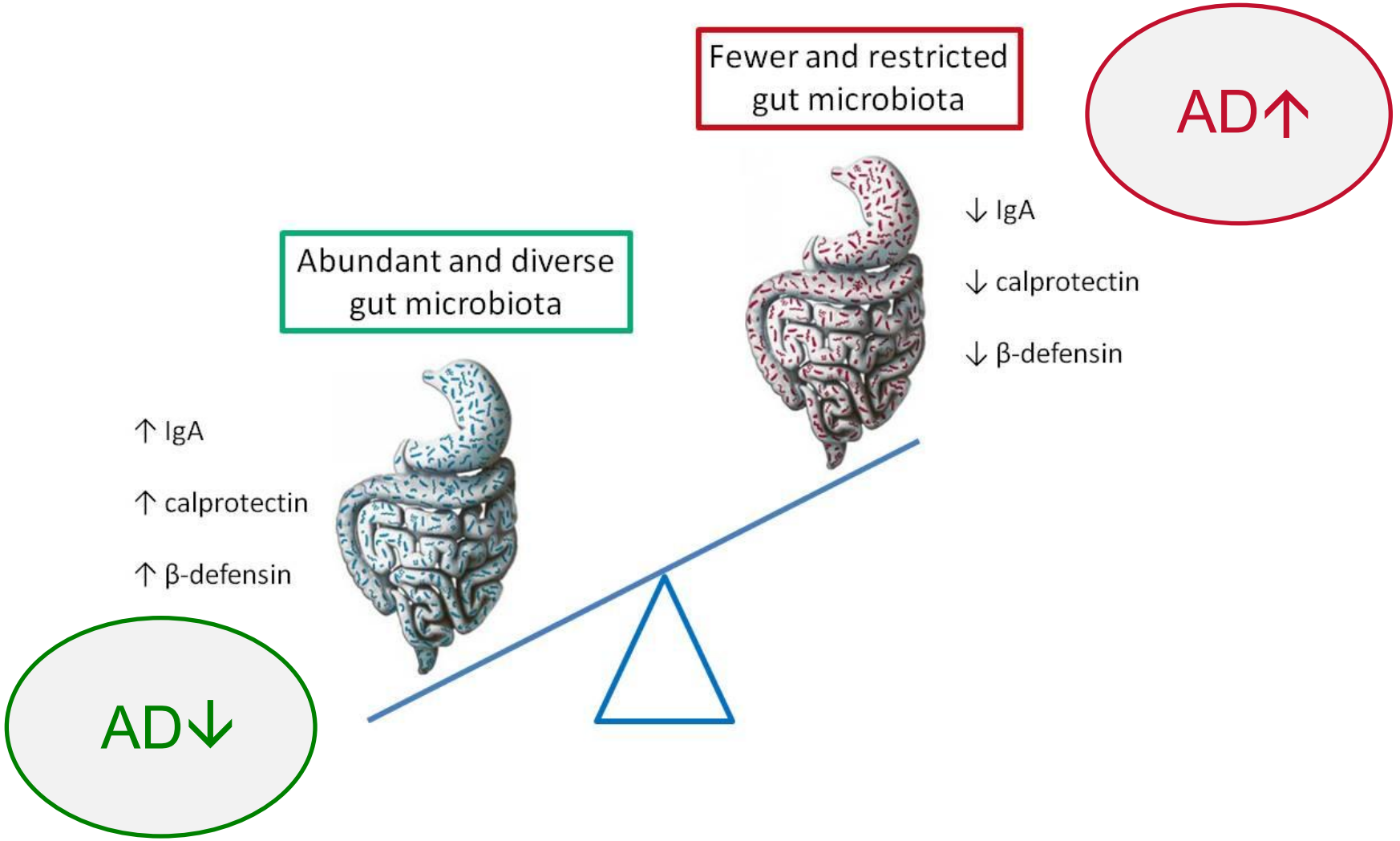
antibiotics (perinatally) ↑

‘education’ of the host immune system in early life



Immune **in**tolerance/allergy

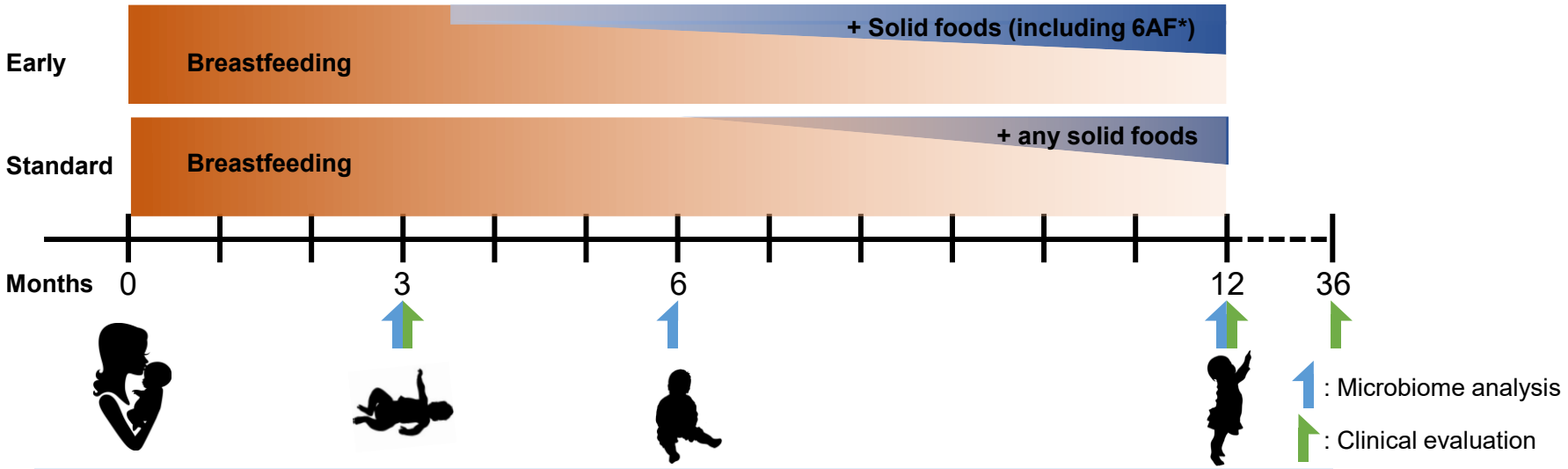
Atopic dermatitis and gut microbiota diversity

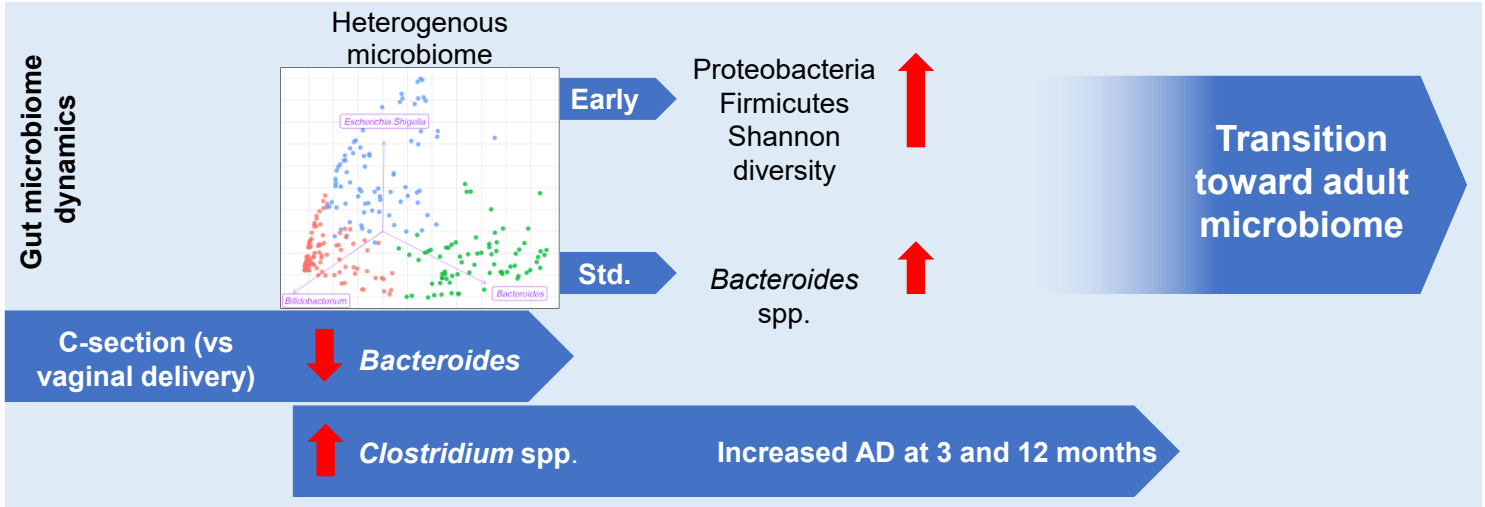


EAT
Enquiring About Tolerance

RCT, n>1300

Dietary intervention groups:





*6 Allergenic foods (6AF): milk, egg, peanut, sesame, cod fish, wheat

Marrs et al. Flohr *JACI* 2021

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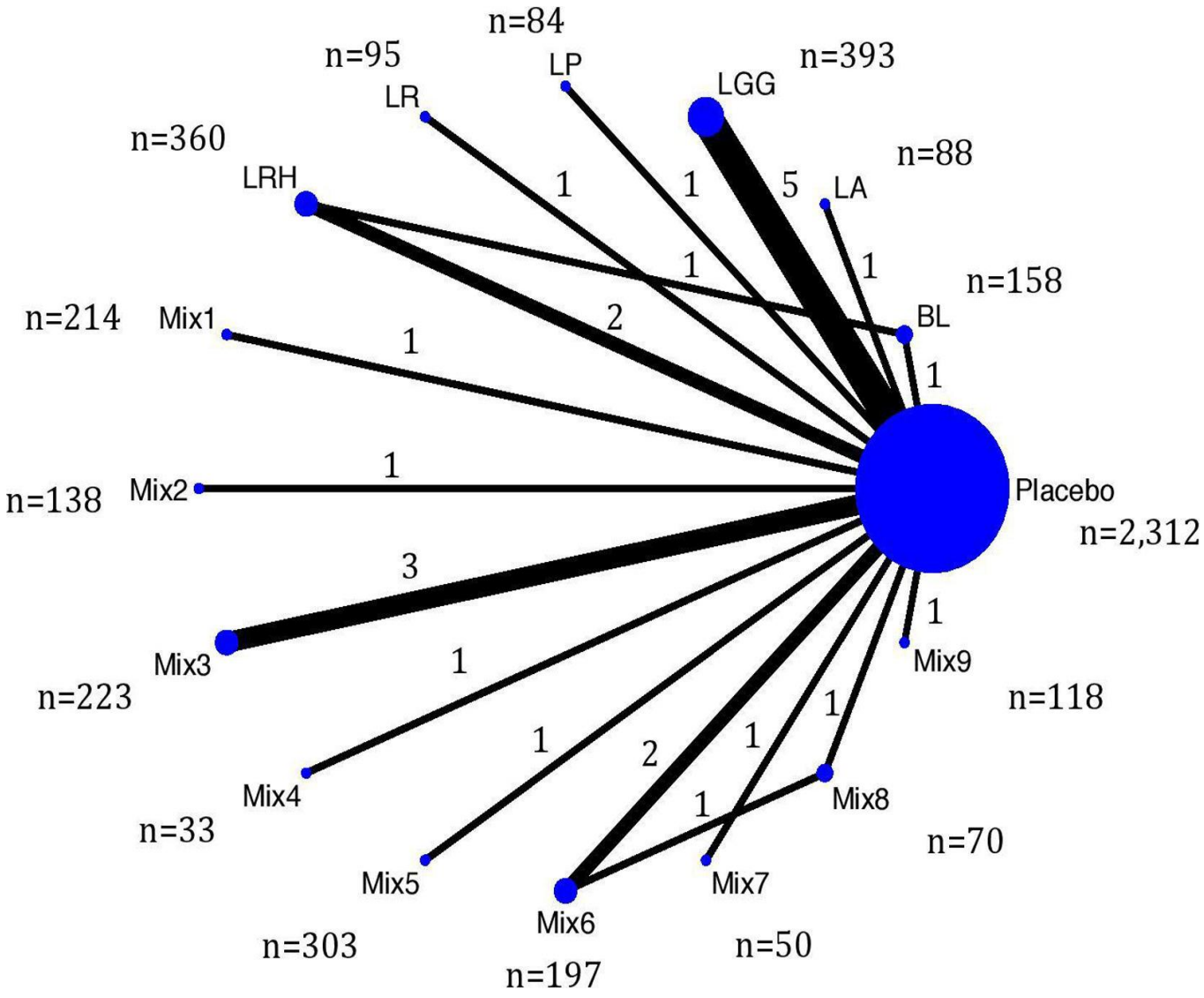
Clinical implications – oral probiotics (live non-pathogenic bacteria)

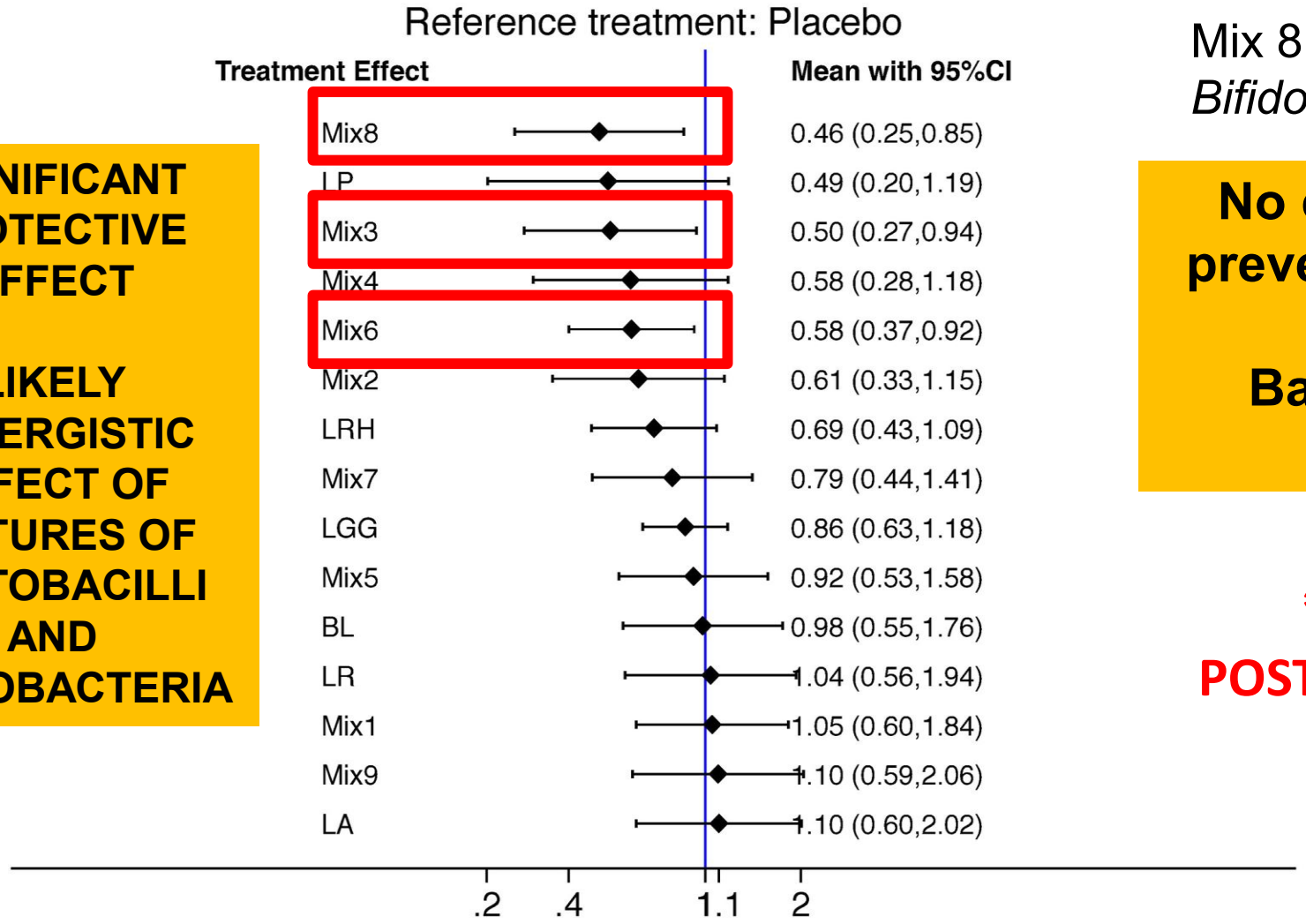
“Comparative effectiveness of probiotic strains on the prevention of pediatric atopic dermatitis: A systematic review and network meta-analysis”



- Many studies
- Methodologically diverse
- Testing different interventions
- Few head-to-head trials
- NMA allows indirect comparison

Tan-Lim et al. *Pediatric Allergy Immunology* 2021

Comparative effectiveness of probiotic strains on the prevention of atopic dermatitis: network meta-analysis



SIGNIFICANT PROTECTIVE EFFECT

LIKELY SYNERGISTIC EFFECT OF MIXTURES OF LACTOBACILLI AND BIFIDOBACTERIA

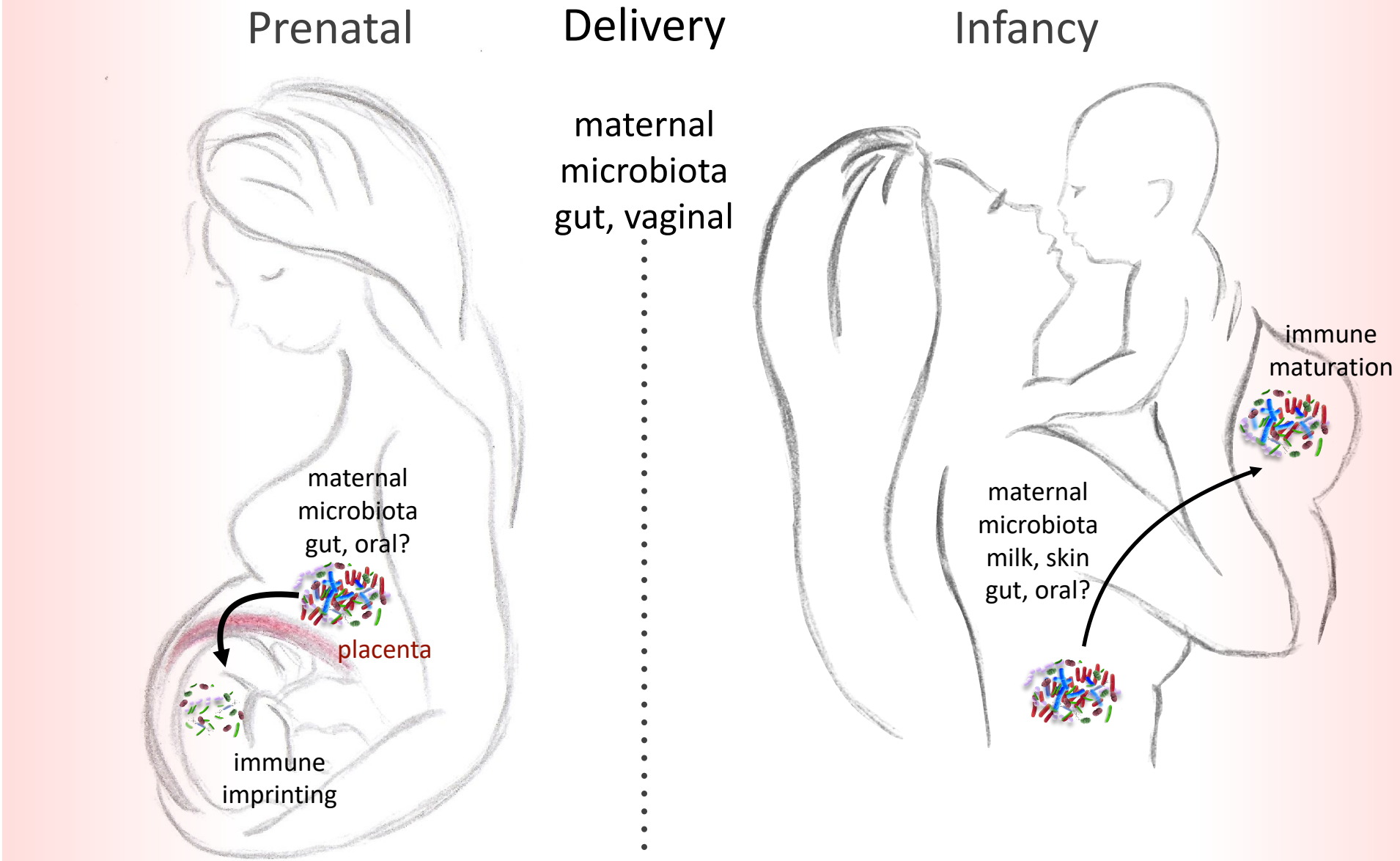
Mix 8: *Lactobacillus casei*, *Bifidobacterium longum*

No convincing evidence for preventative role of prebiotics

Barbarot et al. ISAD 2024

NEEDS BOTH PRE- AND POSTNATAL SUPPLEMENTATION

Tan-Lim et al. *Pediatric Allergy Immunology* 2021

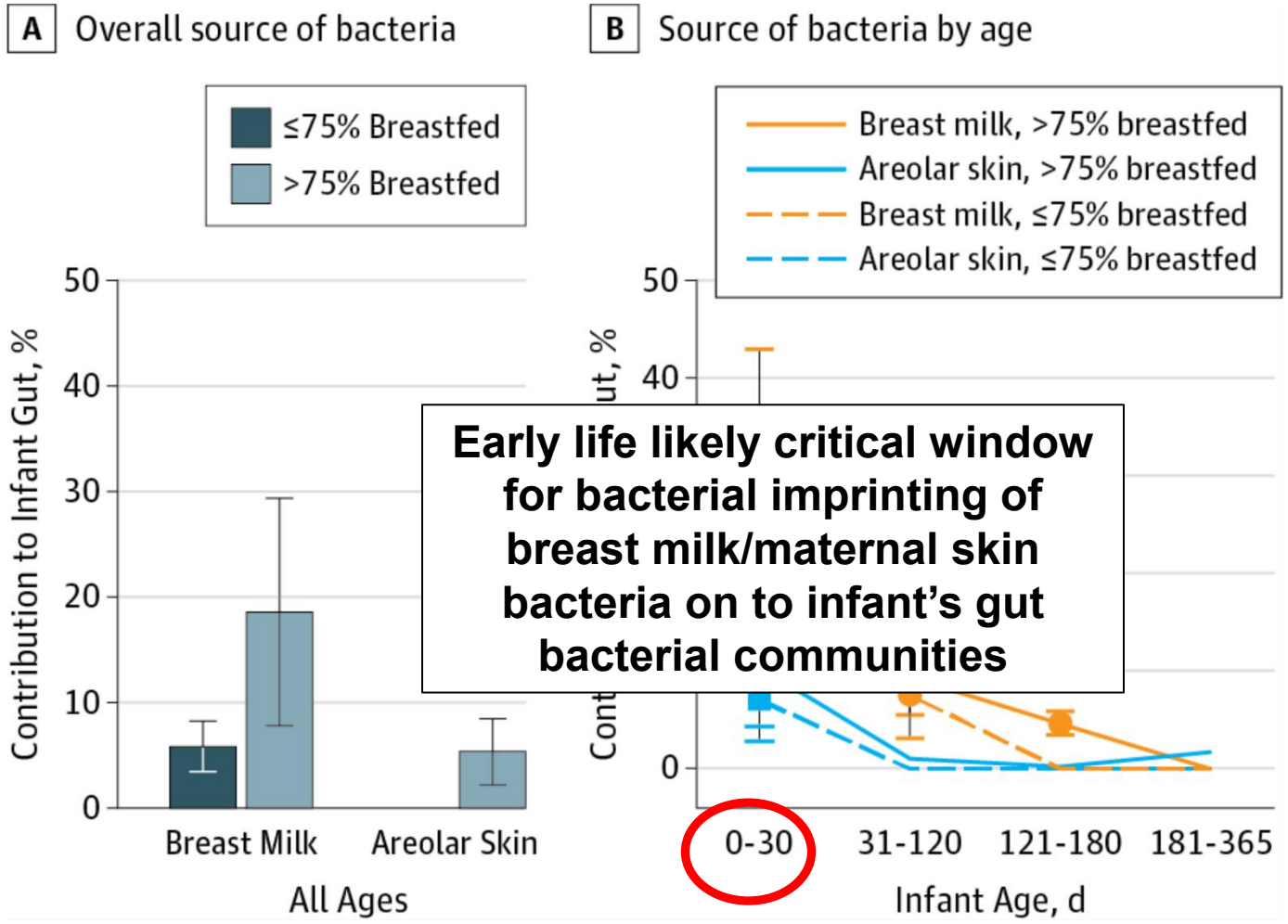


Priming of the immune system during the perinatal period

The JAMA Network

Association Between Breast Milk Bacterial Communities and Establishment and Development of the Infant Gut Microbiome

Pannaraj et al. *JAMA Pediatr* 2017;171:647-654



Early life likely critical window for bacterial imprinting of breast milk/maternal skin bacteria on to infant's gut bacterial communities

N=107 healthy mother-infant pairs

Higher contribution to child's gut microbiome from breastmilk > areolar skin in predominantly breastfed infants

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- **Breastfeeding**
- Strengthening the skin barrier
- Water hardness

Exclusive breastfeeding does **not** significantly impact on atopic dermatitis risk

Multiple studies & systematic reviews

…but what about *ANY* breastfeeding?

→ Clinical trial assessing the effect of breastfeeding

(WHO breastfeeding promotion on postnatal wards)

- Cluster randomization of 31 maternity hospitals

(half used WHO breastfeeding support programme)

- >17,000 healthy newborns

BELARUS – LOWEST BREASTFEEDING RATE IN THE WORLD

Belarus

Promotion of breastfeeding protects against AD into teenage years

Outcome 54% ↓ risk of atopic dermatitis on skin examination (adjusted OR = 0.46, 0.25-0.86)

- **Confirmed findings from infant follow up (*JAMA* 2001)**
- **No additional benefit of exclusive breastfeeding > 3 months**

➢ **infant feeding guidelines have been updated internationally**

Flohr et al. *JAMA Pediatr* 2017

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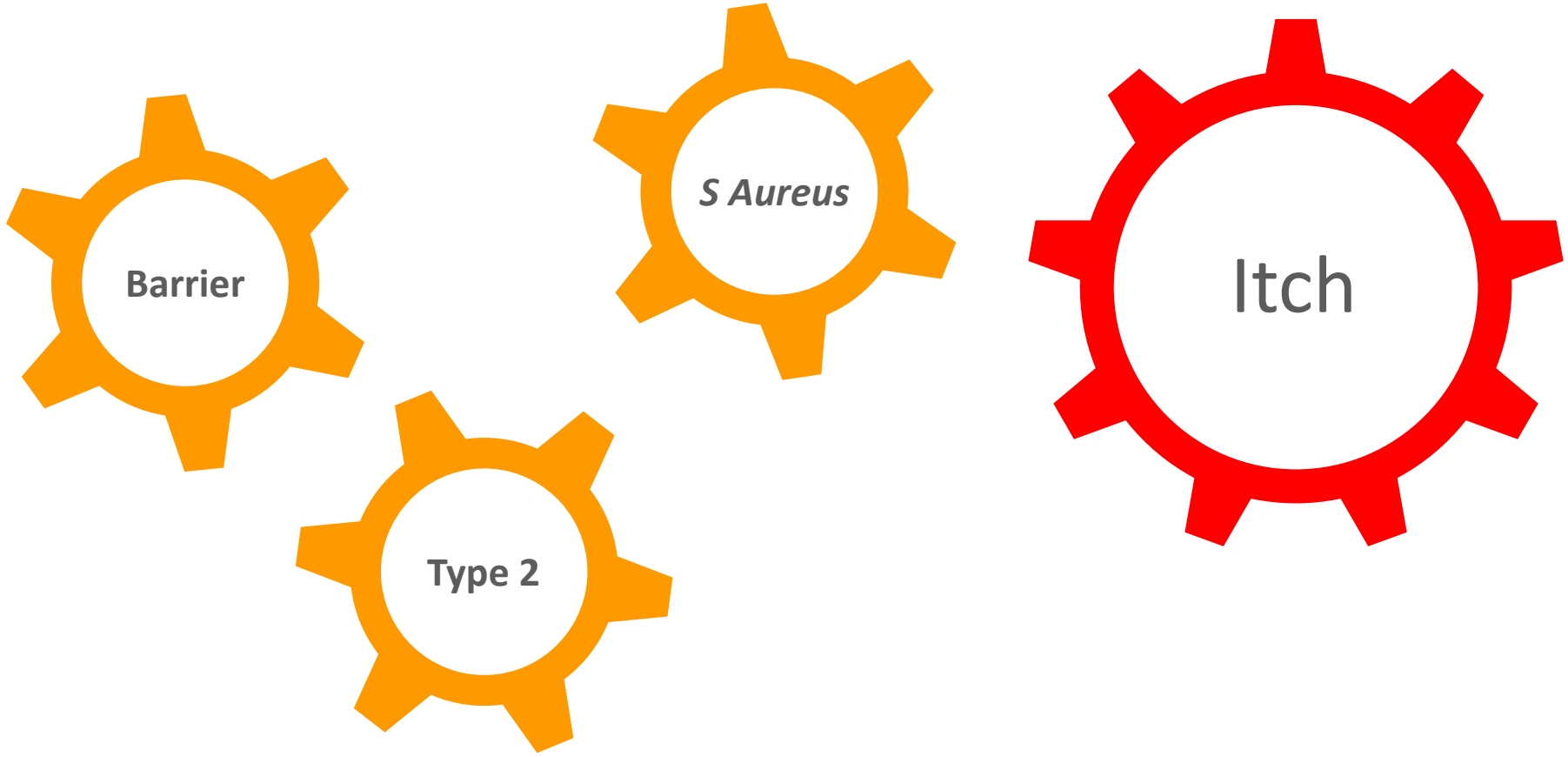
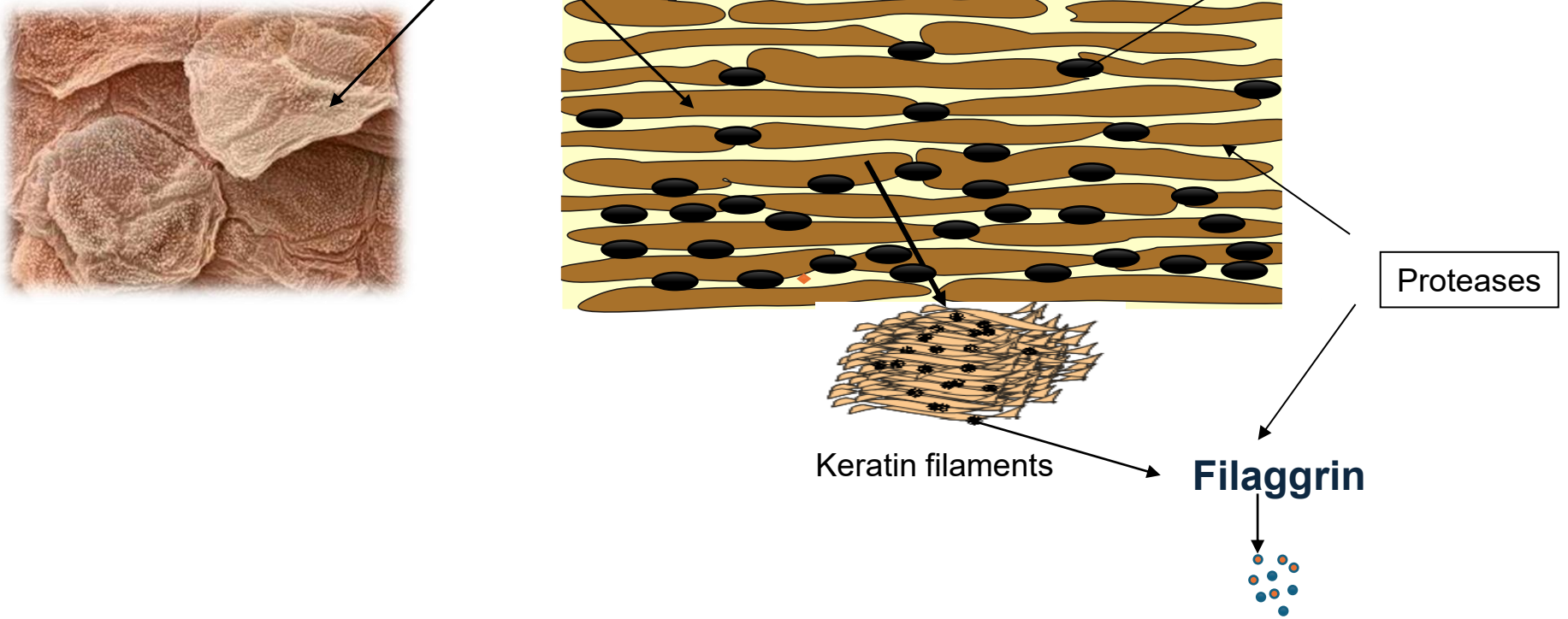
AD: Complex and interacting pathogenesis

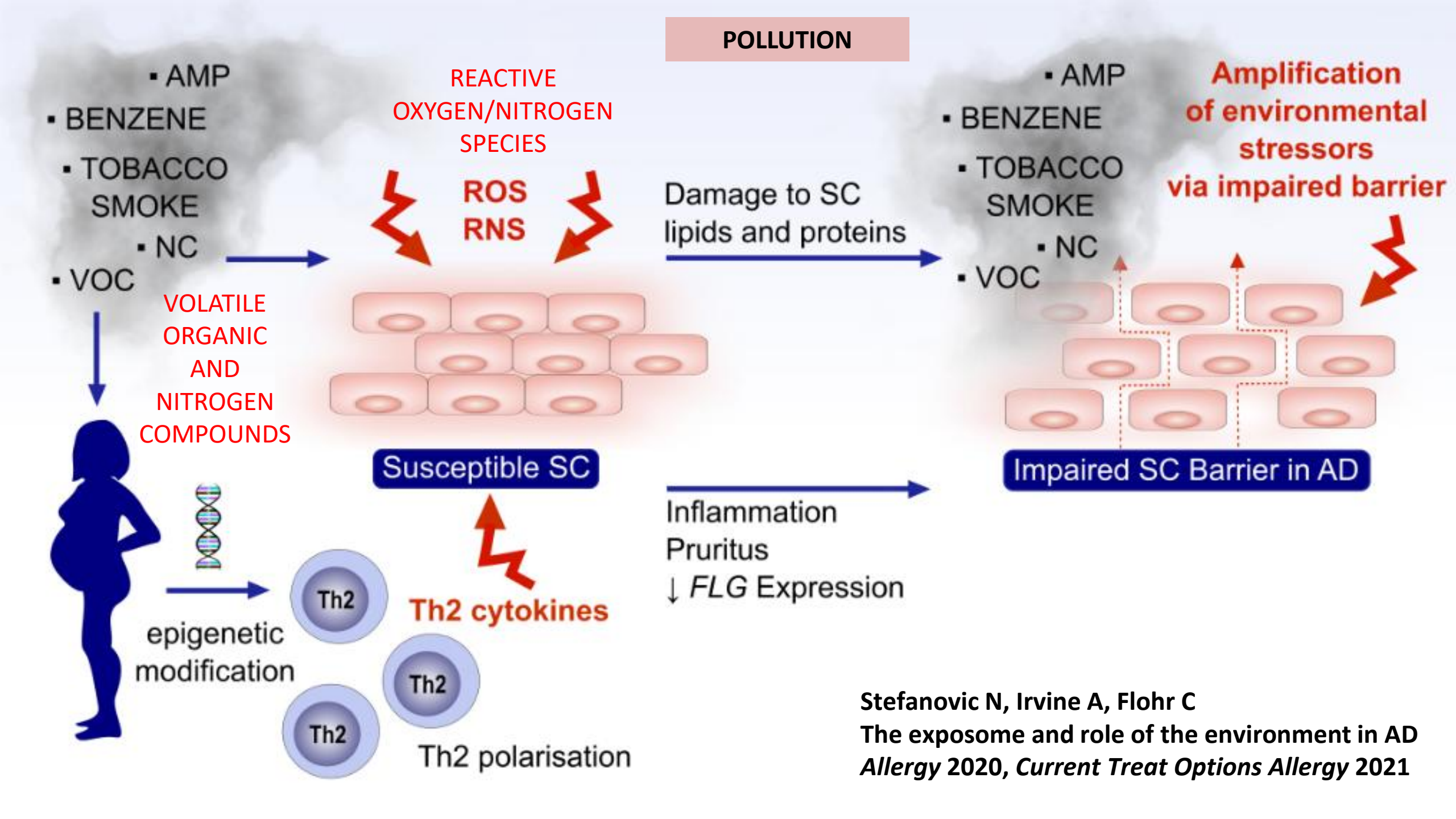


The physical barrier

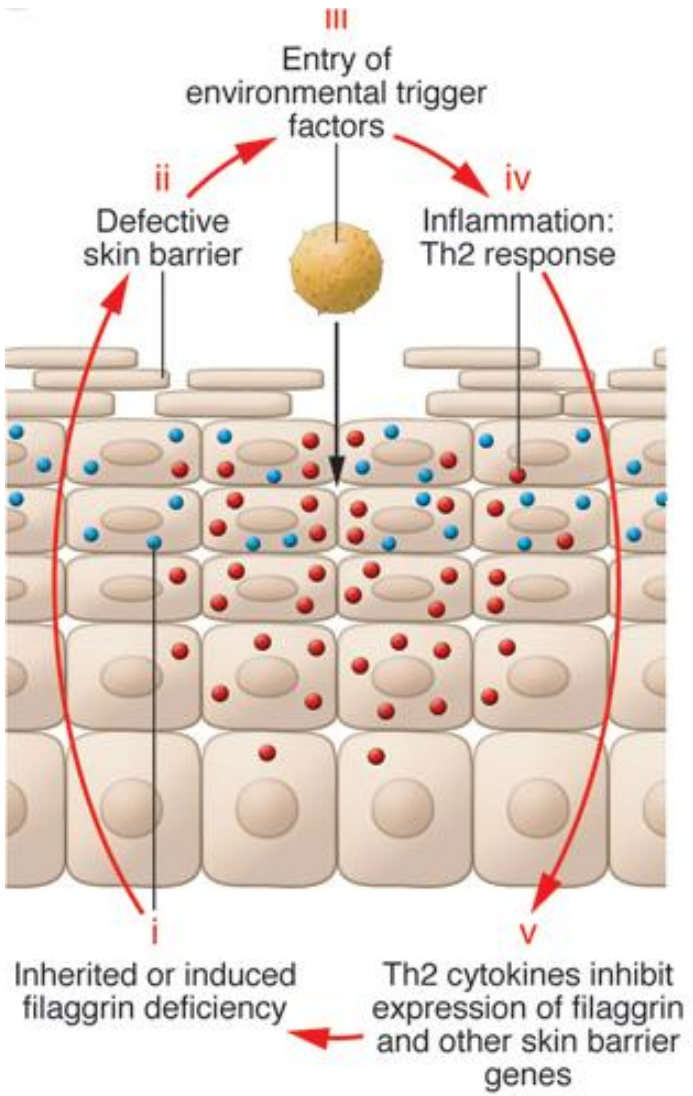


Filaggrin degradation products
Natural moisturizing factors (NMF)

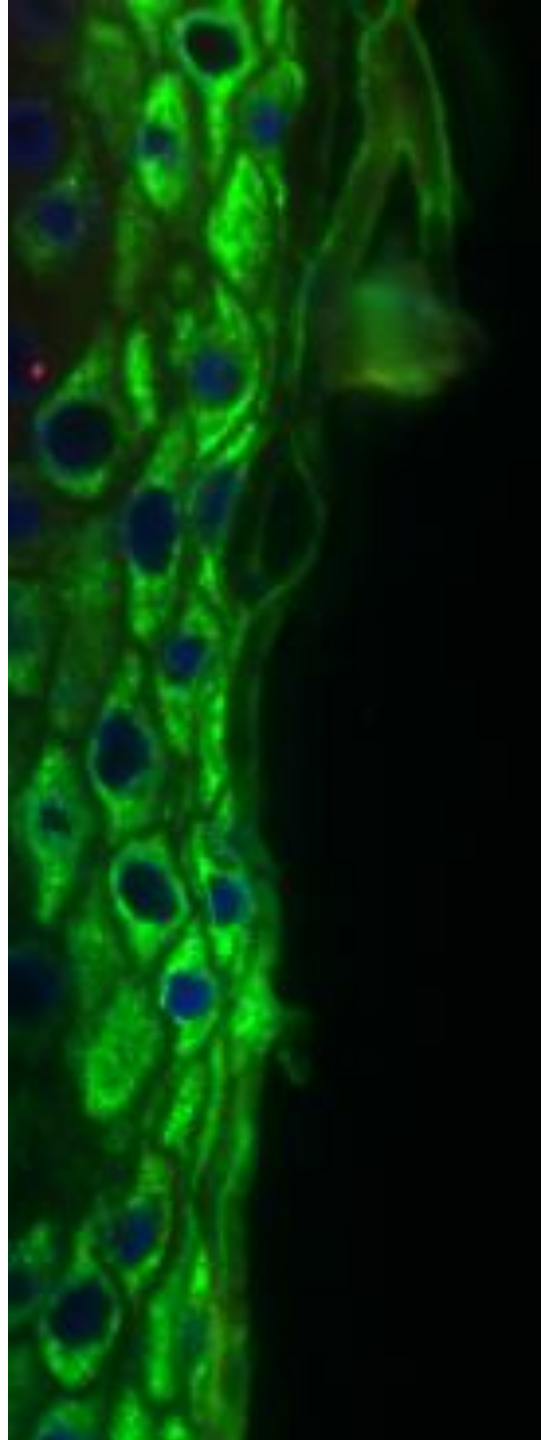
A second hit on the barrier in atopic dermatitis



Stefanovic N, Irvine A, Flohr C
The exposome and role of the environment in AD
***Allergy* 2020, *Current Treat Options Allergy* 2021**

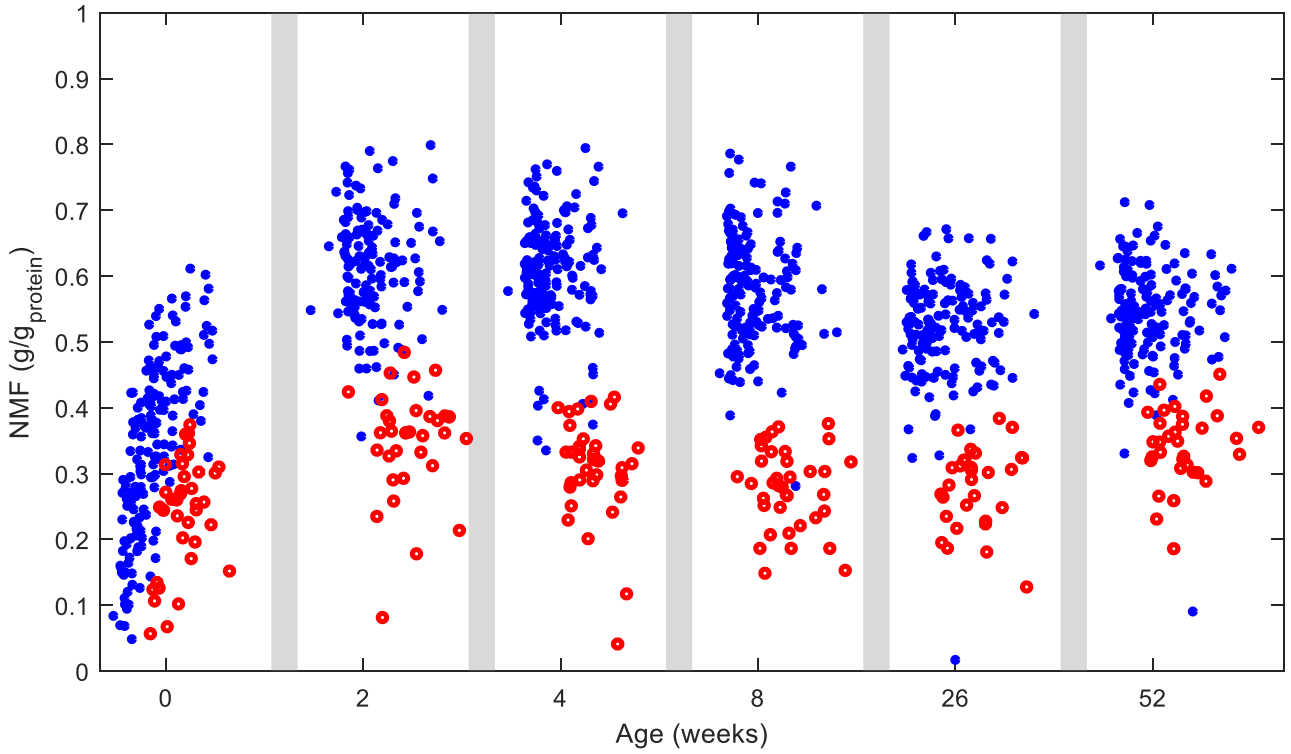


Type 2 inflammation further impairs the skin barrier



Early life events at the skin barrier: pre-clinical atopic dermatitis

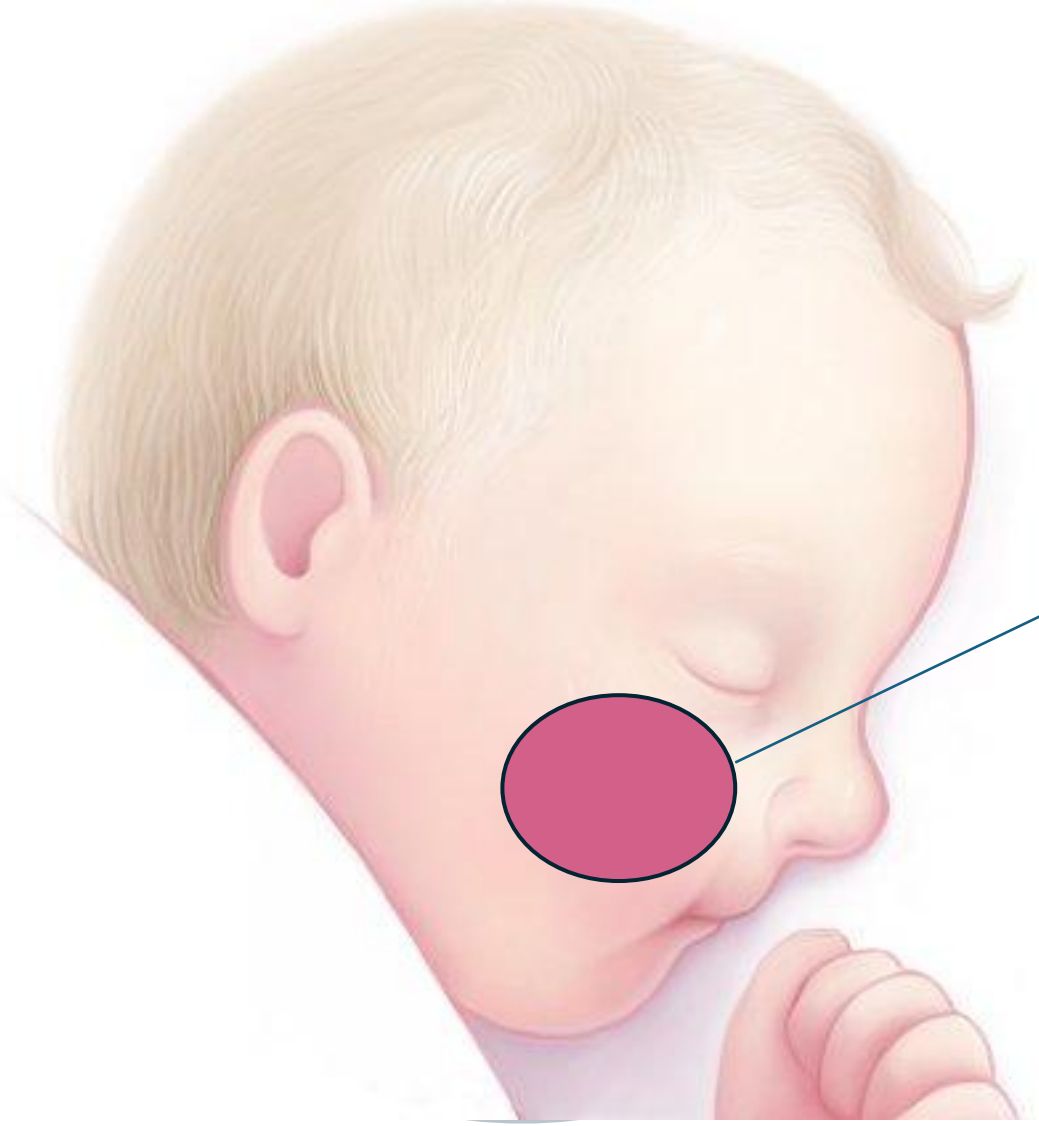
NMF shows rapid post natal changes and identifies newborns with a LoF-FLG

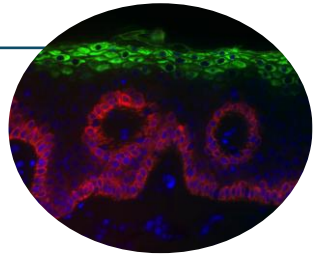


wild type-FLG

LoF-FLG mutation carriers

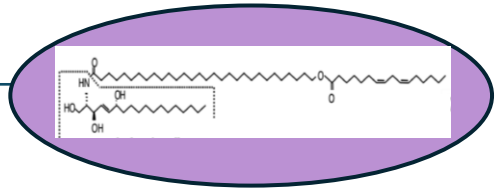
Courtesy Alan Irvine



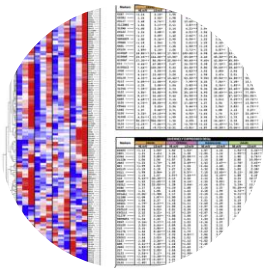


Low

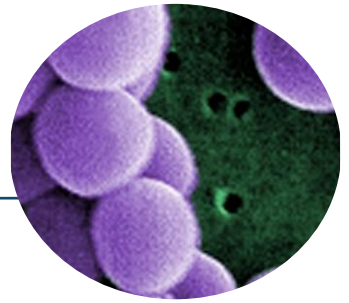
NMF



Ceramide and free base alterations



Type 2 immune skewing



Microbiome alterations

Courtesy Alan Irvine

Does regular emollient application prevent AD?

1394 newborns ('high risk')

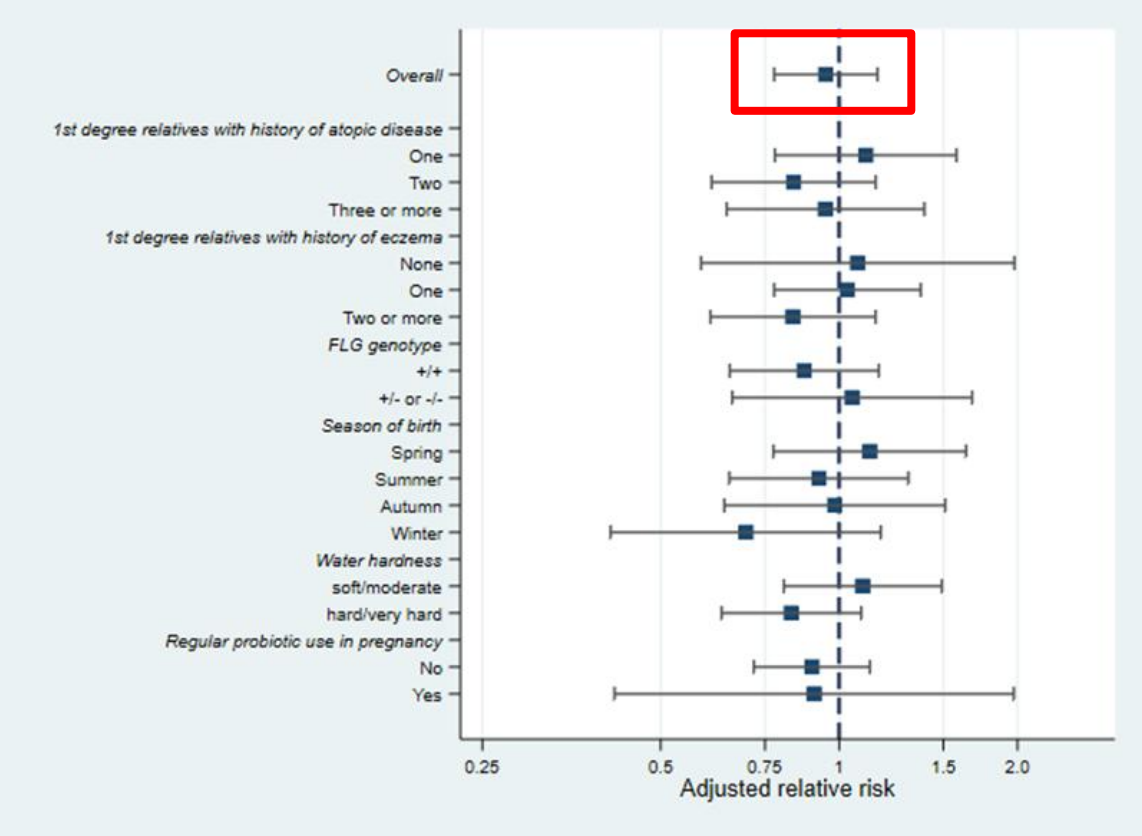
regular emollient application vs standard care

2 small RCTs, n=118 and 124 (*JACI* 2014)
≤50% ↓risk first year of life
(high risk infants)

- **effective, safe and cheap (→ BEEP)**

Barrier Enhancement Eczema Prevention (BEEP) Trial

Chalmers et al. *Lancet* 2020



Relative risk of atopic dermatitis by 2 yrs

Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial

Joanne R Chalmers, Rachel H Haines, Lucy E Bradshaw, Alan A Montgomery, Kim S Thomas, Sara J Brown, Matthew J Ridd, Sandra Lawton, Eric L Simpson, Michael J Cork, Tracey H Sach, Carsten Flohr, Eleanor J Mitchell, Richard Swinden, Stella Tarr, Susan Davies-Jones, Nicola Jay, Maeve M Kelleher, Michael R Perkin, Robert J Boyle, Hywel C Williams on behalf of the BEEP study team

Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial

Håvard Ove Skjerven, Eva Maria Rehbinder, Riyas Vettukattil, Marissa LeBlanc, Berit Granum, Guttorm Haugen, Gunilla Hedlin, Linn Landrø, Benjamin J Marsland, Knut Rudi, Kathrine Dønvold Sjøborg, Cilla Söderhäll, Anne Cathrine Staff, Kai-Håkon Carlsen, Anna Asarnoj, Karen Eline Stensby Bains, Oda C Lødrup Carlsen, Kim M Advocaat Endre, Peder Annæus Granlund, Johanne Uthus Hermansen, Hrefna Katrín Gudmundsdóttir, Katarina Hilde, Geir Håland, Ina Kreyberg, Inge Christoffer Olsen, Caroline-Aleksi Olsson Mägi, Live Solveig Nordhagen, Carina Madelen Saunders, Ingebjørg Skrindo, Sandra G Tedner, Magdalena R Værnesbranden, Johanna Wiik, Christine Monceyron Jonassen, Björn Nordlund, Karin C Lødrup Carlsen

Prevent ADALL - SIMILAR RESULTS TO BEEP

STANDARD EMOLLIENTS DO NOT HELP TO PREVENT AD

Can regular moisturisation in early life prevent AD?

7 trials (1489 participants) contributed to meta-analysis

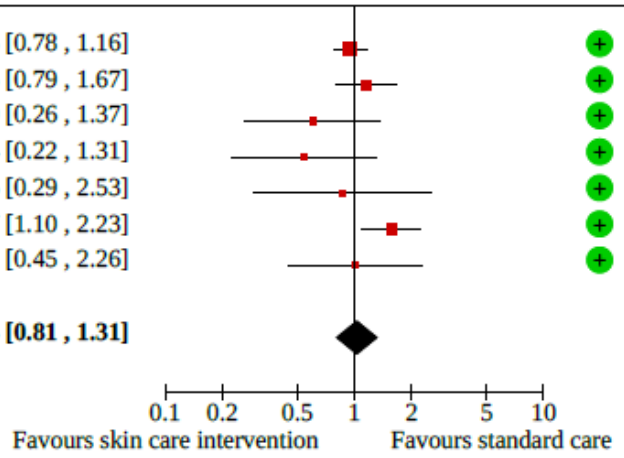
Analysis 1.1. Comparison 1: Skin care intervention versus standard skin care or no skin care intervention, Outcome 1: Eczema by 1 to 3 years

Study or Subgroup	log[RR]	SE	Skin care intervention Total	Standard care Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Chalmers 2020	-0.05	0.1	598	612	32.1%	0.95 [0.78 , 1.16]	+	+	+	+	+	+
Dissanayake 2019	0.14	0.19	232	223	20.7%	1.15 [0.79 , 1.67]	+	+	+	+	+	+
Lowe 2018a	-0.51	0.42	38	36	7.1%	0.60 [0.26 , 1.37]	+	+	+	+	+	+
McClanahan 2019	-0.61	0.45	31	29	6.3%	0.54 [0.22 , 1.31]	+	+	?	+	+	?
NCT03376243	-0.15	0.55	22	27	4.5%	0.86 [0.29 , 2.53]	+	+	?	+	+	?
Skjerven 2020	0.45	0.18	499	572	21.8%	1.57 [1.10 , 2.23]	+	+	?	+	+	?
Yonezawa 2018	0.01	0.41	69	87	7.4%	1.01 [0.45 , 2.26]	+	+	?	?	+	?
Total (95% CI)			**1489**	**1586**	**100.0%**	**1.03 [0.81 , 1.31]**						

Heterogeneity: Tau² = 0.04; Chi² = 10.20, df = 6 (P = 0.12); I² = 41%

Test for overall effect: Z = 0.24 (P = 0.81)

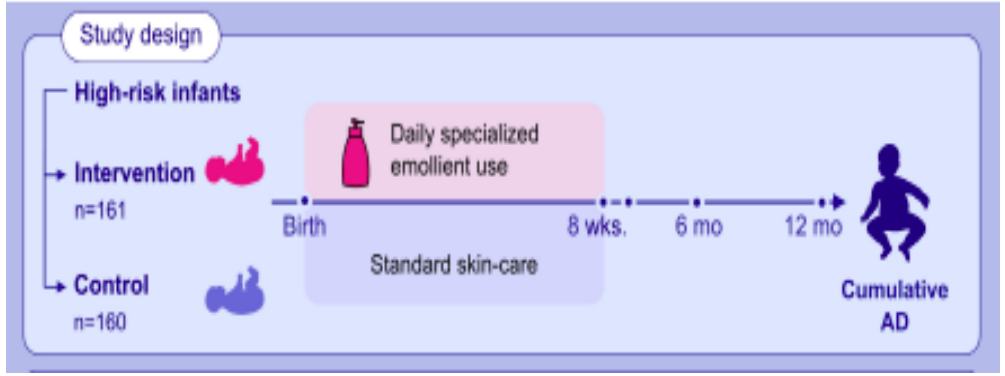
Test for subgroup differences: Not applicable

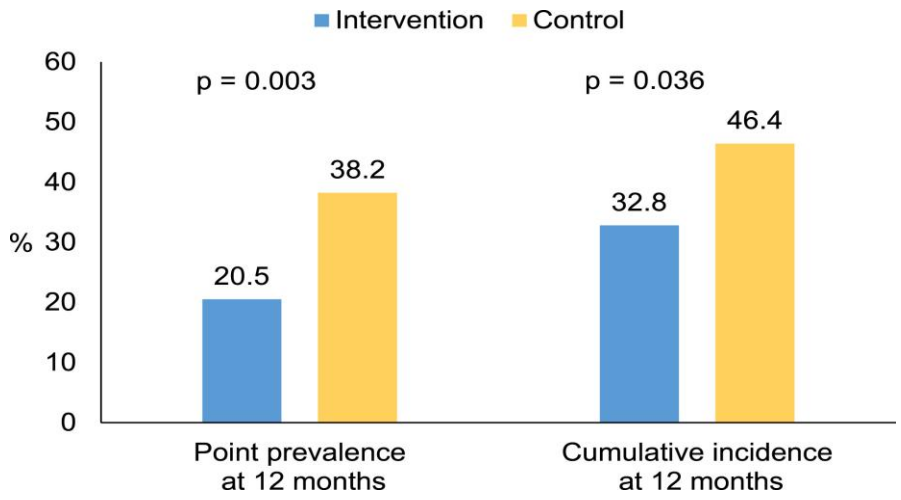


Kelleher MM, et al. Skincare interventions in infants for preventing eczema and food allergy: A Cochrane systematic review and individual participant data meta-analysis. Cochrane Library 2022

STOP-AD study - Ní Chaoimh *et al.* Allergy 2023;78:984–994

- Single-centre randomized controlled clinical trial (n=321)
- Term infants identified as **high risk for AD** (family history)
  - **Intervention group:**
    - twice-daily emollient application for the first 8 weeks after birth (AVEENO® Baby Daily Care Baby Gentle Wash; J&J)
  - **Control group:**
    - standard skin care

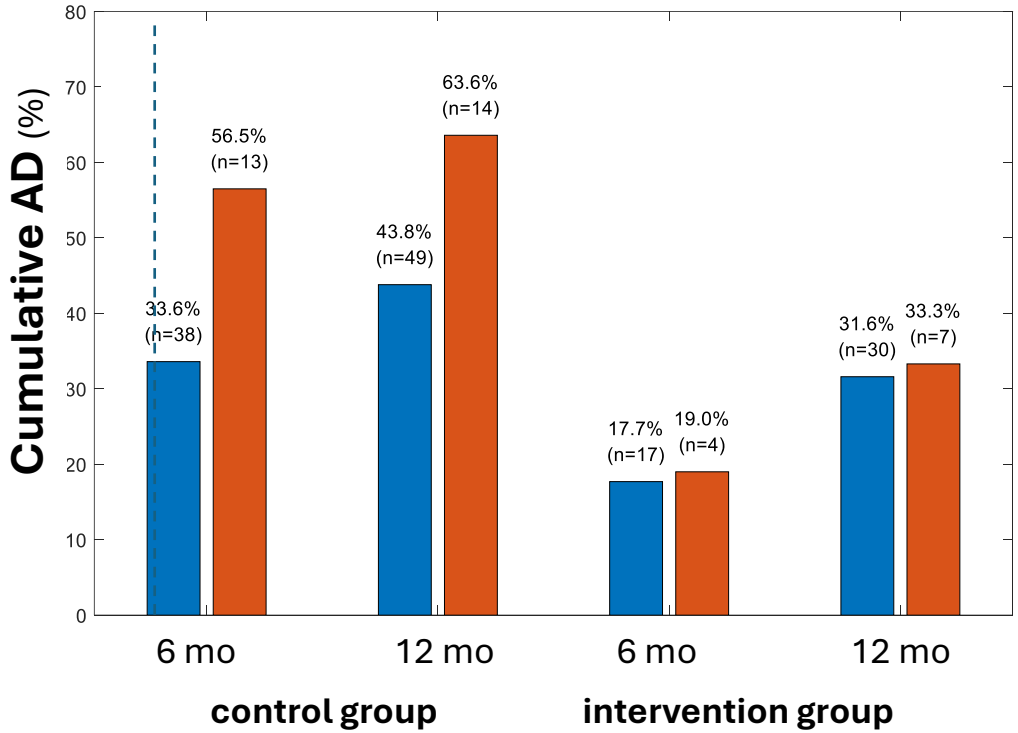




Early initiation of daily specialized emollient use until 2 months reduces the incidence of AD in the first year of life in high-risk infants.

- **33% in the intervention group vs. 46% in the control group**

STOP-AD study – FLG genotype stratification



wild type FLG

LoF-FLG mutation carrier

Short term emollient treatment appears to:

- reduce AD incidence in first year of life
- take away the “extra risk of AD-development” for FLG-mutation carriers

No effect for UK refinement criteria

614 infants – daily full-body emollient within first 9 wks of life

633 infants – standard of care

n = 1247

Follow-up at 24 months

Cumulative AD 36.1% (SE, 2.1%)

Cumulative AD 43.0% (SE, 2.1%)

RR=0.84 (95%CI, 0.73-0.97)

Protective effect **dog-ownership**, '**low-risk**' infants

OR=0.68; 95%CI, 0.50-0.90

Simpson et al., JAMA, 2025

Re-opening the discussion around using emollients to prevent AD for all

Conclusions primary prevention through emollients

- Intervention trials have shown different results
- Systematic review shows no effect, pending update
- Timing of intervention & emollient characteristics may make a difference
- Debate on prevention is not yet fully over

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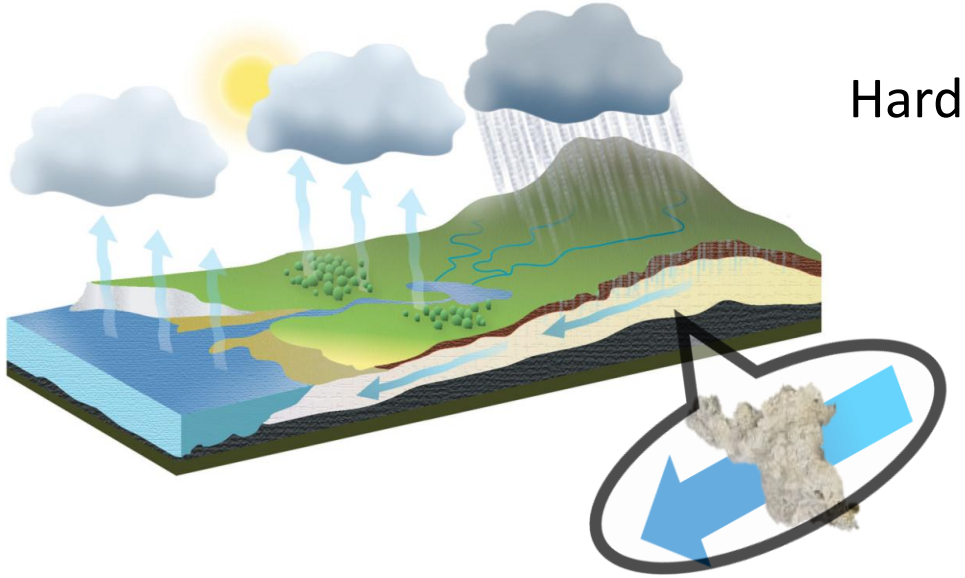
- **Water hardness**

WATER HARDNESS

Hard water and atopic dermatitis

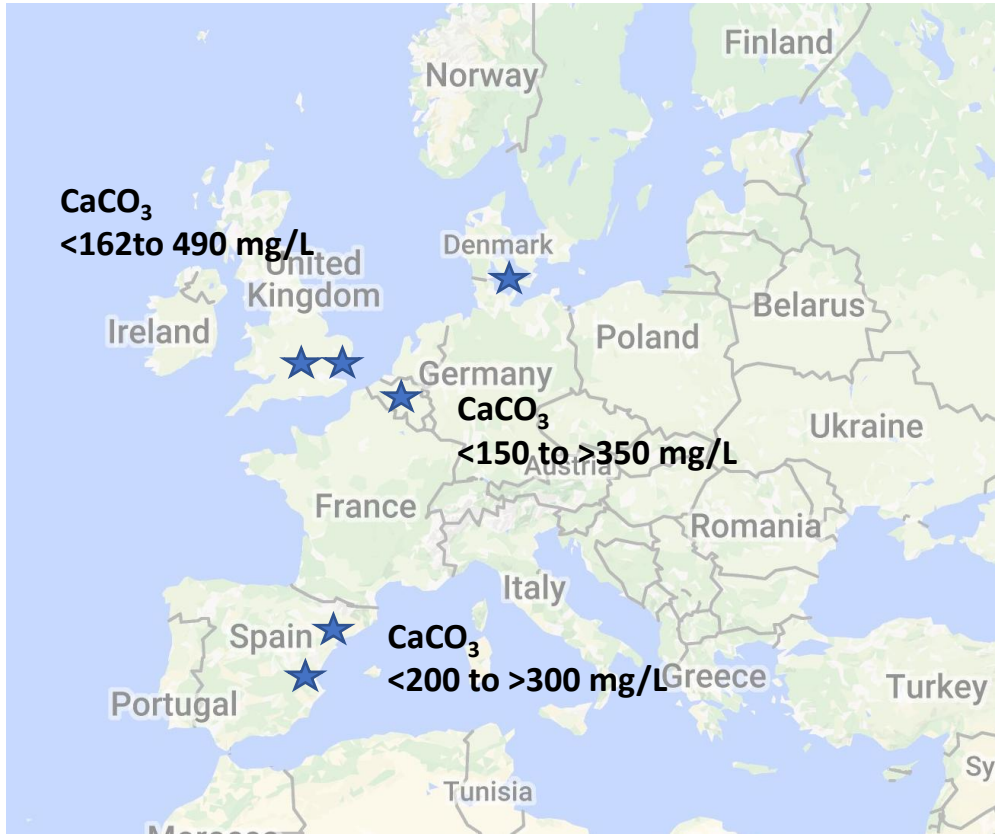


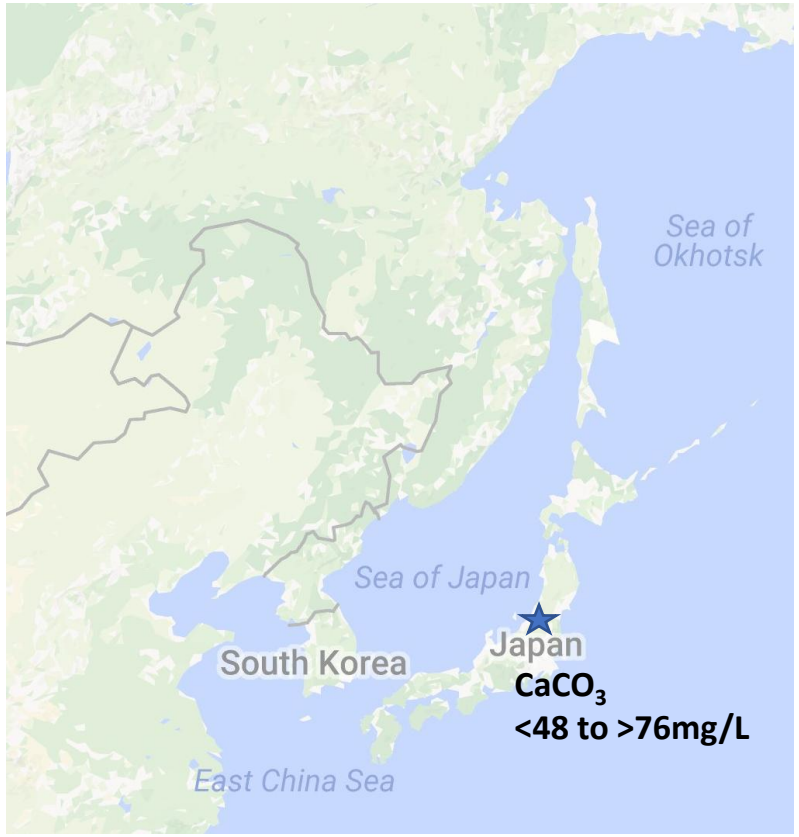
Hard water has a high calcium carbonate content

The effects:

- leaves limescale deposits
- stains and damaged appliances
- block pipes and boilers
- skin pH ▲ → skin barrier breakdown

Association between water hardness and atopic dermatitis has been observed in cross-sectional studies – school children





UK (McNally) OR 1.28 (1.04-1.58)	Japan (Miyake) OR 1.12 (1.06-1.18)	Spain (Arnedo-Pena) OR 1.58 (1.04-2.39)	Belgium (Chaumont) OR 1.97 (0.97-3.96)
1998	2004	2007	2012

Jabbar-Lopez et al. Flohr, *CEA* 2020

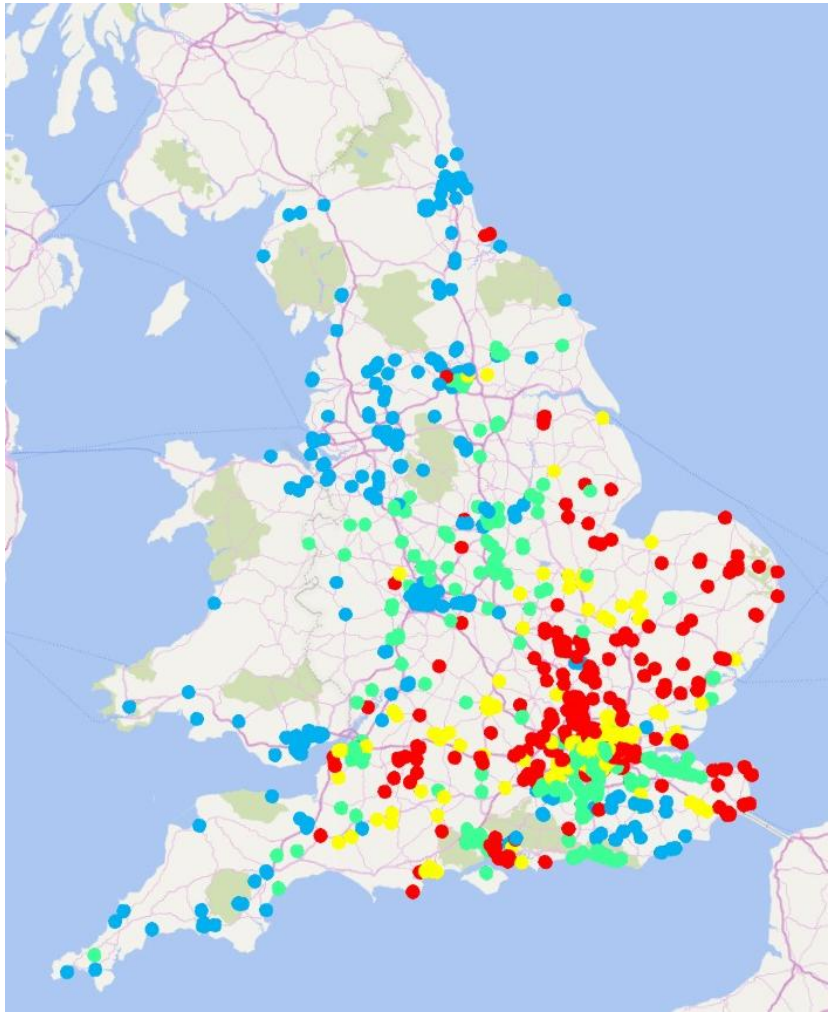
Domestic water hardness varied widely amongst EAT participants – early life

EAT Enquiring About Tolerance

KING'S College LONDON

Calcium Carbonate (mg/L)

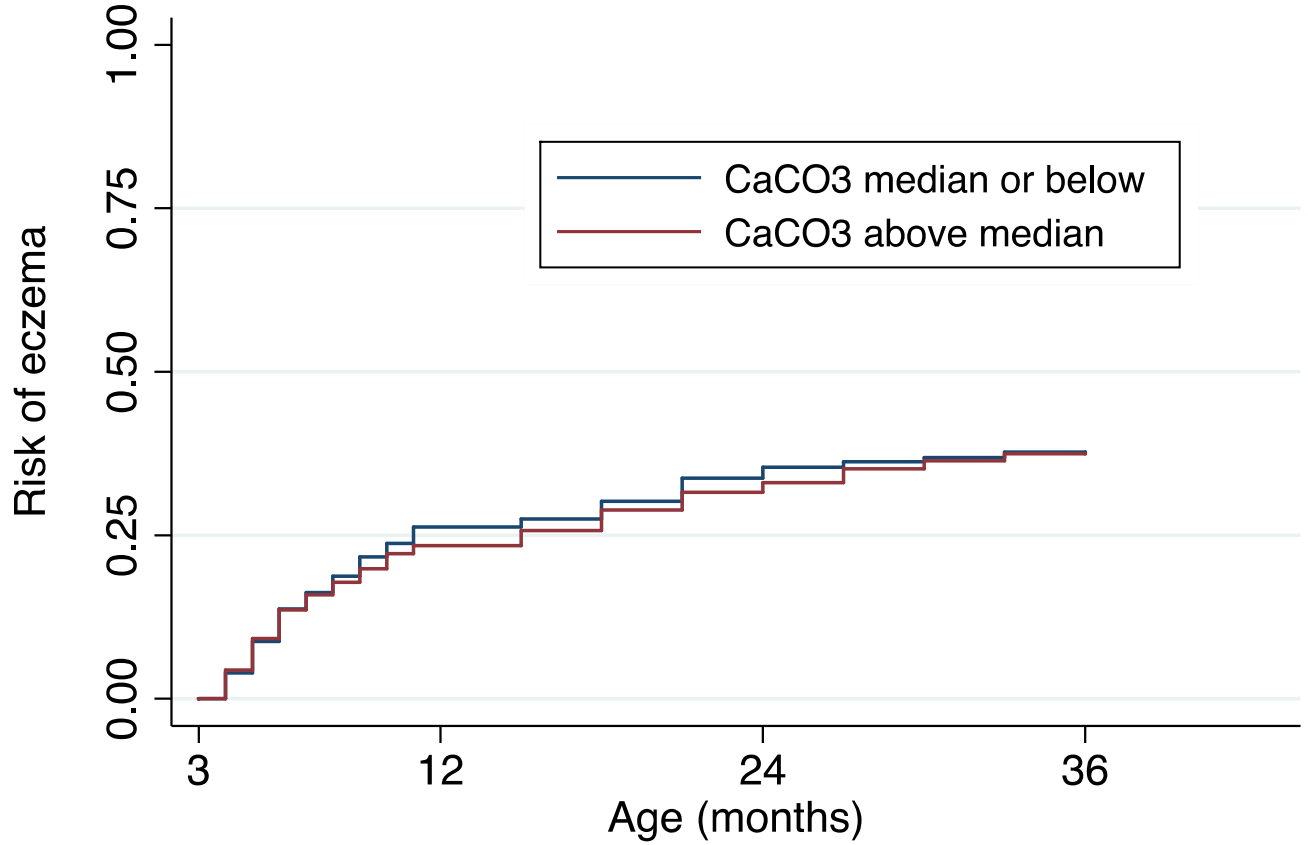
- 0-162.99
- 163-257.5
- 257.6-286.5
- 286.6-500



N=1,303
Age 3mths →

Perkin et al Flohr, *JACI* 2016

No overall effect of water hardness on atopic dermatitis risk



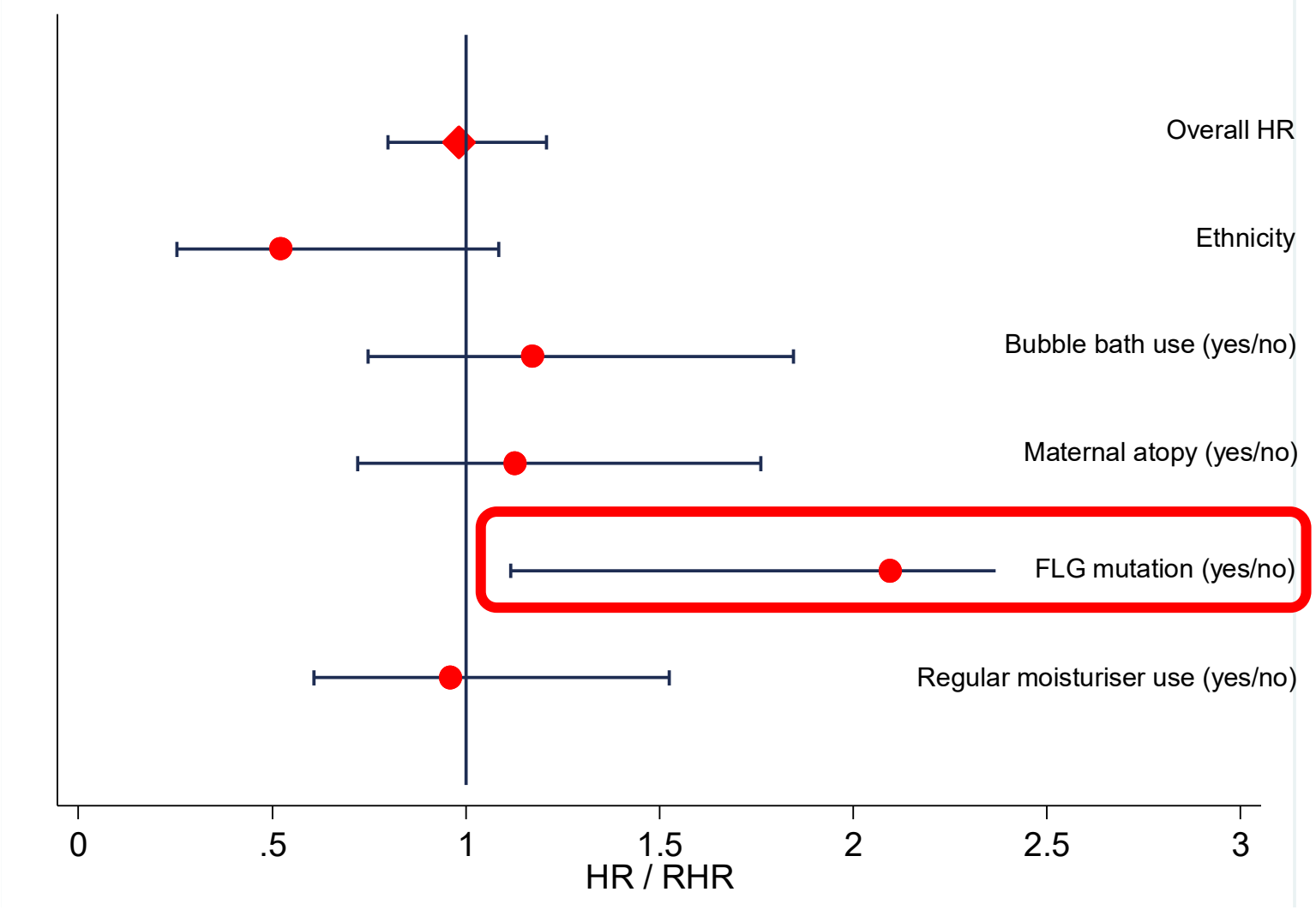
Number at risk				
CaCO3 median/below	480	354	318	303
CaCO3 above median	478	366	327	304

Adjusted* hazard ratio
0.97 (0.78, 1.21)

*adjusted for:
home location (rural/urban)
maternal education,
indices of deprivation,
ethnicity

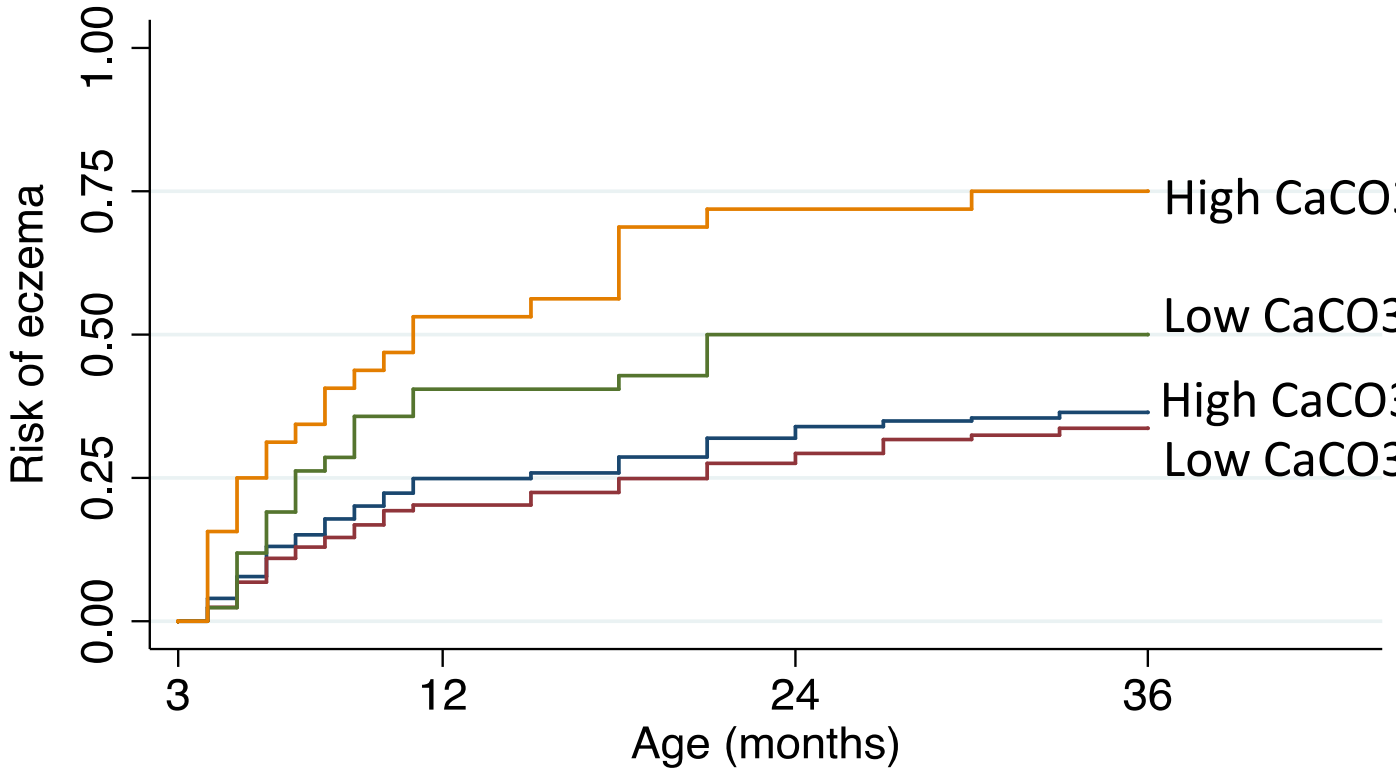
Jabbar-Lopez et al. Flohr, *BJD* 2020

Effect modification by *FLG* mutation status but not other key covariates



Jabbar-Lopez et al. Flohr, *BJD* 2020

Hard water increases risk of atopic dermatitis in FLG loss of function carriers – G*E interaction



High CaCO3/FLG mutation **HR 2.70 (1.73, 4.20)**

Low CaCO3/FLG mutation **HR 1.45 (0.91, 2.30)**

High CaCO3/normal FLG **HR 0.92 (0.72, 1.16)**

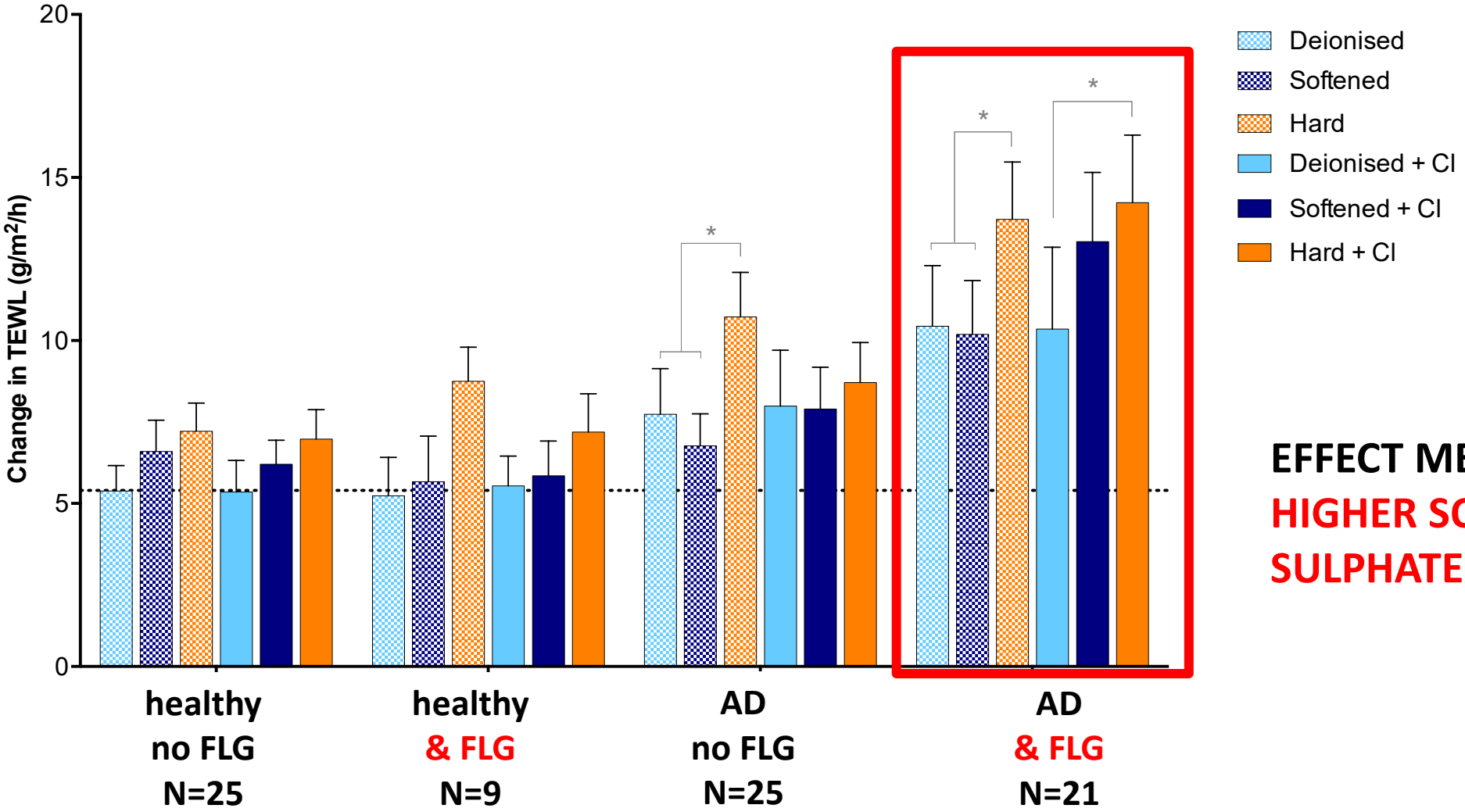
Low CaCO3/normal FLG **HR 1**

***P*<0.001 (log rank)**

Number at risk				
CaCO3 Low/FLG norm	398	299	271	257
CaCO3 High/FLG norm	410	327	297	277
CaCO3 Low/FLG mut	42	25	21	21
CaCO3 High/FLG mut	32	15	9	8

Jabbar-Lopez et al Flohr, *BJD* 2020

Increased skin barrier dysfunction in AD patients with *FLG* mutations exposed to hard water – washing experiments



EFFECT MEDIATED BY HIGHER SODIUM LAURYL SULPHATE DEPOSITION

Danby et al. Flohr, Cork, *JID* 2017

Softened Water Eczema Prevention Trial

or

Atopic dermatitis

Birth-6 months

Clinicaltrials.gov NCT03270566

SOFTER trial - main findings

SOFTER

STUDY DESIGN

Pregnant woman with personal history of atopy

living in domestic hard water areas ($CaCO_3$ > 250 mg/L)

Study enrolment and follow up period: Feb 2018 to Oct 2019

INTERVENTION PROTOCOL

1:1

usual domestic hard water n=40

ion-exchange water softener n=40

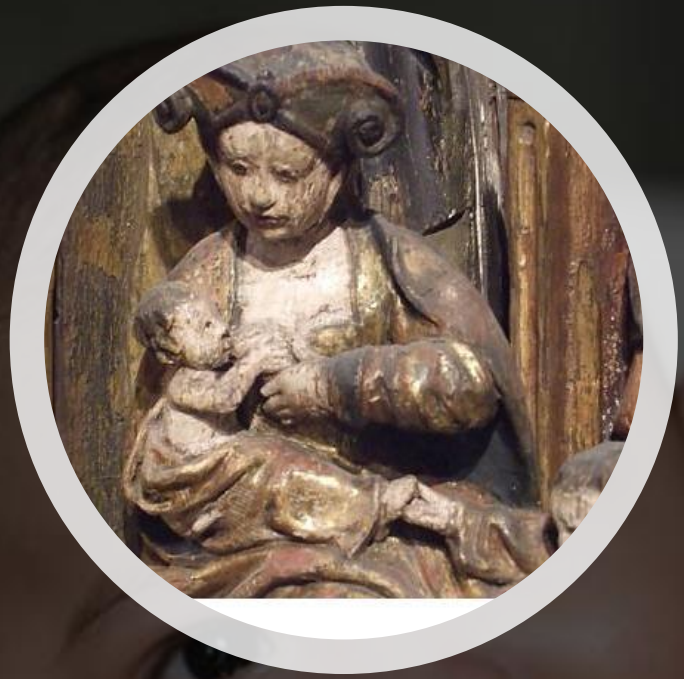
Primary endpoint : proportion of eligible families screened who were willing and able to be randomised

Infants followed from birth to 6 months of age

- 54% of eligible families were willing and able to be randomised
- All participants found the study acceptable
- By 6 months of age 27 infants developed visible eczema (33% vs 48%) in water softener vs control group
- A lower proportion of infants in the water softener arm had parent-reported, doctor-diagnosed eczema by 6 months compared to the control arm (35% vs 47%)

Pilot trial – not statistically powered
Multicentre definitive RCT required

Ezzamouri et al. Flohr, *Clin Exp Allergy* 2022



Water softener in early life

Perinatal antibiotics use↓


Thank you!