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The skin barrier topic is still open!

Jonathan Hourihane



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Disclosure

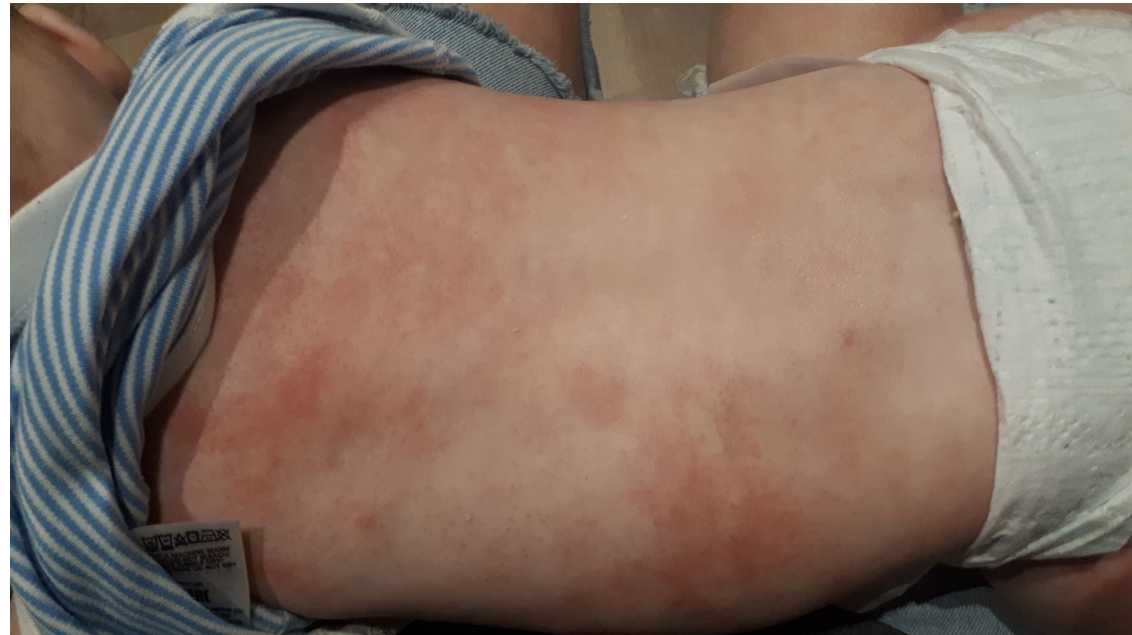
In relation to this presentation, I declare the following, real or perceived conflicts of interest:

Type	Company
Employment full time / part time	Royal College of Surgeons in Ireland and Childrens Health Ireland
Research Grant (P.I., collaborator or consultant; pending and received grants)	Temple St Foundation, Clemens von Pirquet Foundation, National Childrens Research Centre, City of Dublin Skin and Cancer Hospital, Ireland, Johnson&Johnson
Speakers Bureau / Honoraria	DBV Technologies
Ownership interest (stock, stock-options, patent or intellectual property)	Johnson& Johnson
Consultant / advisory board	Aimmune Therapeutics , Johnson&Johnson, Clemens von Pirquet Foundation, Irish Food Allergy Network

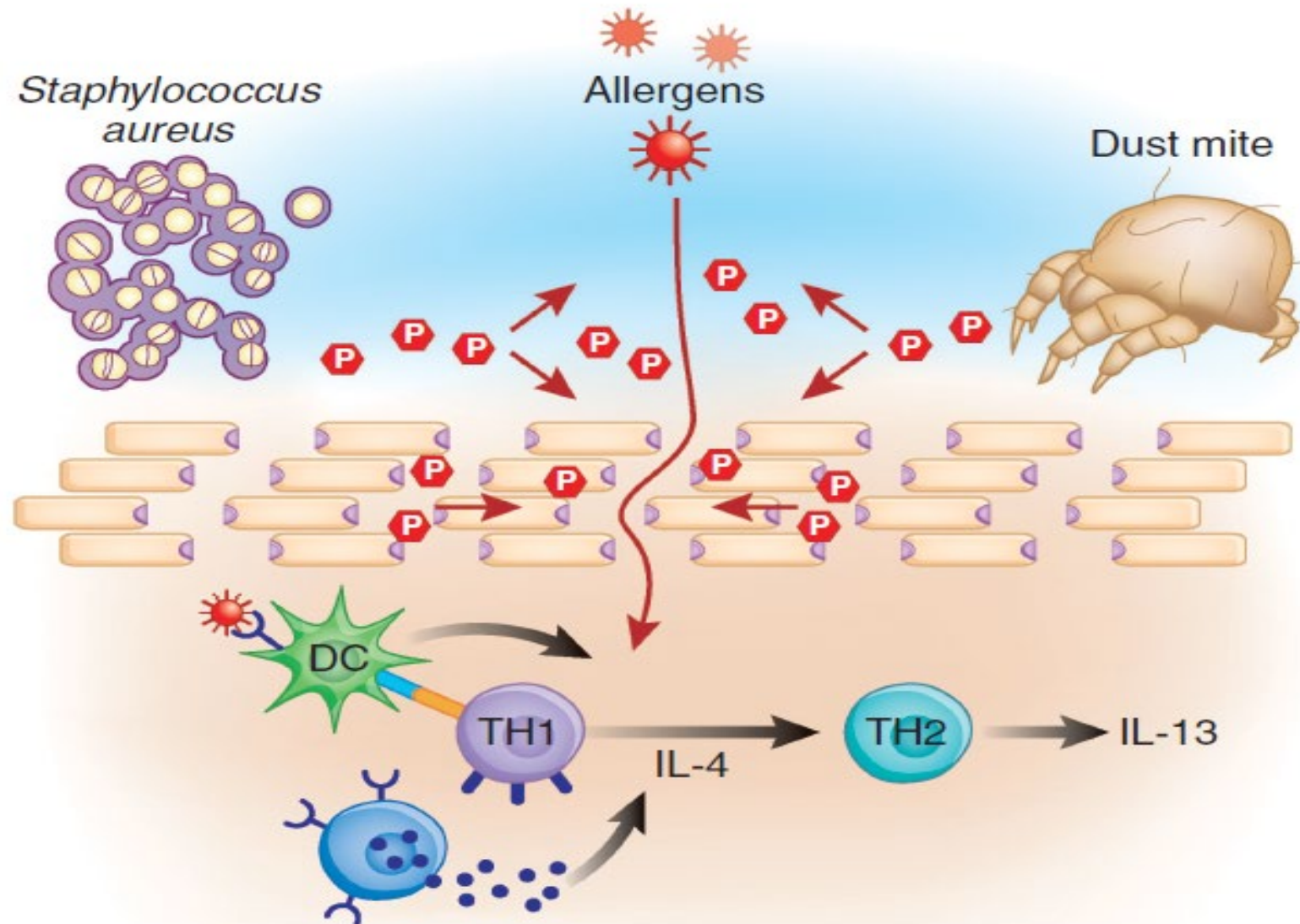
A conflict of interest is any situation in which a speaker or immediate family members have interests, and those may cause a conflict with the current presentation. Conflicts of interest do not preclude the delivery of the talk, but should be explicitly declared. These may include financial interests (eg. owning stocks of a related company, having received honoraria, consultancy fees), research interests (research support by grants or otherwise), organisational interests and gifts.

Atopic Dermatitis (AD)

- Common inflammatory skin disorder
- 30% in children.
- Characterized by intensely itchy skin.
- Psychosocial impact on patients and caregivers
- Complex aetiology
- Atopic diseases rarely occur in isolation.



Defective Skin Barrier in AD



Can emollients in infancy prevent AD?

Atopic dermatitis and skin disease

Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention

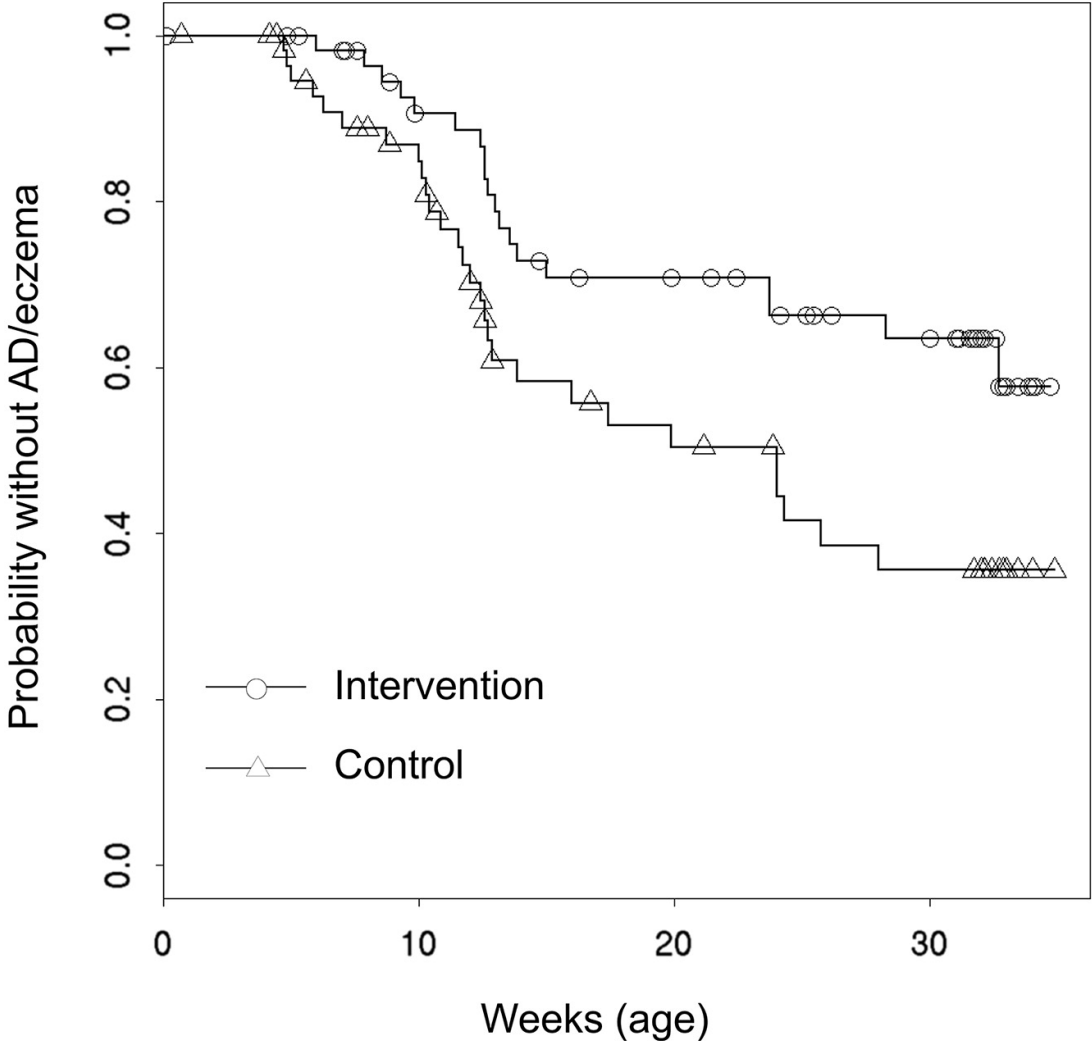
Eric L. Simpson, MD, MCR,^a Joanne R. Chalmers, PhD,^b Jon M. Hanifin, MD,^a Kim S. Thomas, PhD,^b Michael J. Cork, PhD, FRCP,^c W. H. Irwin McLean, FRSE, FMedSci,^d Sara J. Brown, MRCP, MD,^d Zunqiu Chen, MS,^e Yiyi Chen, PhD,^f and Hywel C. Williams, DSc, FMedSci^b *Portland, Ore, and Nottingham, Sheffield, and Dundee, United Kingdom*

Application of moisturizer to neonates prevents development of atopic dermatitis

Kenta Horimukai, MD,^{a*} Kumiko Morita, MD,^{a*} Masami Narita, MD, PhD,^a Mai Kondo, MD,^a Hiroshi Kitazawa, MD, PhD,^a Makoto Nozaki, MD,^b Yukiko Shigematsu, MD,^b Kazue Yoshida, MD, PhD,^b Hironori Niizeki, MD, PhD,^b Ken-ichiro Motomura, MD,^c Haruhiko Sago, MD, PhD,^c Tetsuya Takimoto, MD, PhD,^d Eisuke Inoue, PhD,^d Norio Kamemura, PhD,^e Hiroshi Kido, MD, PhD,^e Junzo Hisatsune, PhD,^f Motoyuki Sugai, DDS, PhD,^f Hiroyuki Murota, MD, PhD,^g Ichiro Katayama, MD, PhD,^g Takashi Sasaki, PhD,^h Masayuki Amagai, MD, PhD,^h Hideaki Morita, MD, PhD,ⁱ Akio Matsuda, PhD,ⁱ Kenji Matsumoto, MD, PhD,ⁱ Hirohisa Saito, MD, PhD,ⁱ and Yukihiro Ohya, MD, PhD^a *Tokyo, Tokushima, Hiroshima, and Osaka, Japan*

- Daily emollient use from birth to 6 -8 months reduced AD risk by up to 50%

Neonatal moisturisation decreases eczema

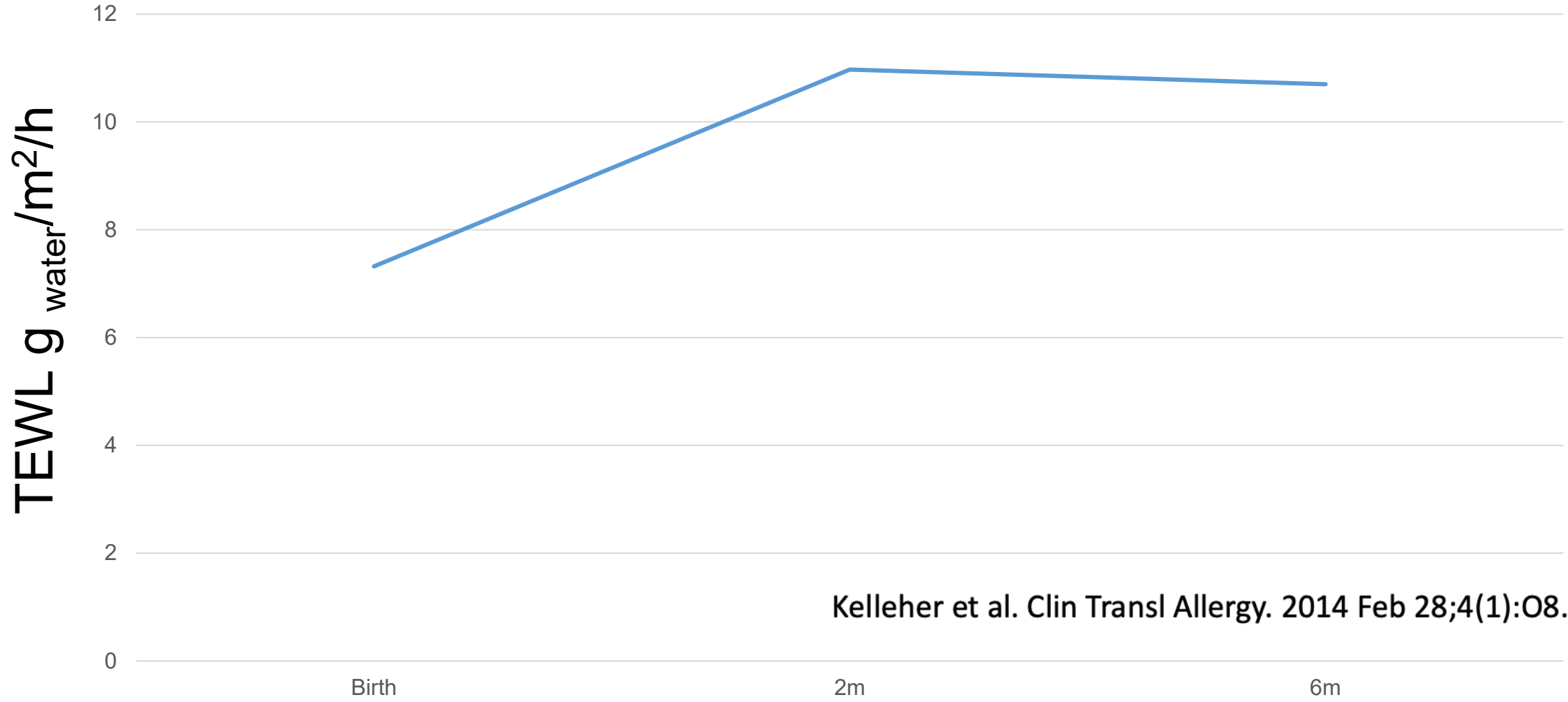


Trans-epidermal water loss (TEWL)

- Increased from birth to 2 months but stabilised thereafter
- An earlier window for skin barrier protection, from birth to 2 months, may exist



TEWL increases from birth to 2m and then stabilizes to 6m



Kelleher et al. Clin Transl Allergy. 2014 Feb 28;4(1):O8.

Measurement of Skin Barrier structure and Function

Natural Moisturizing Factor (NMF) Measurements

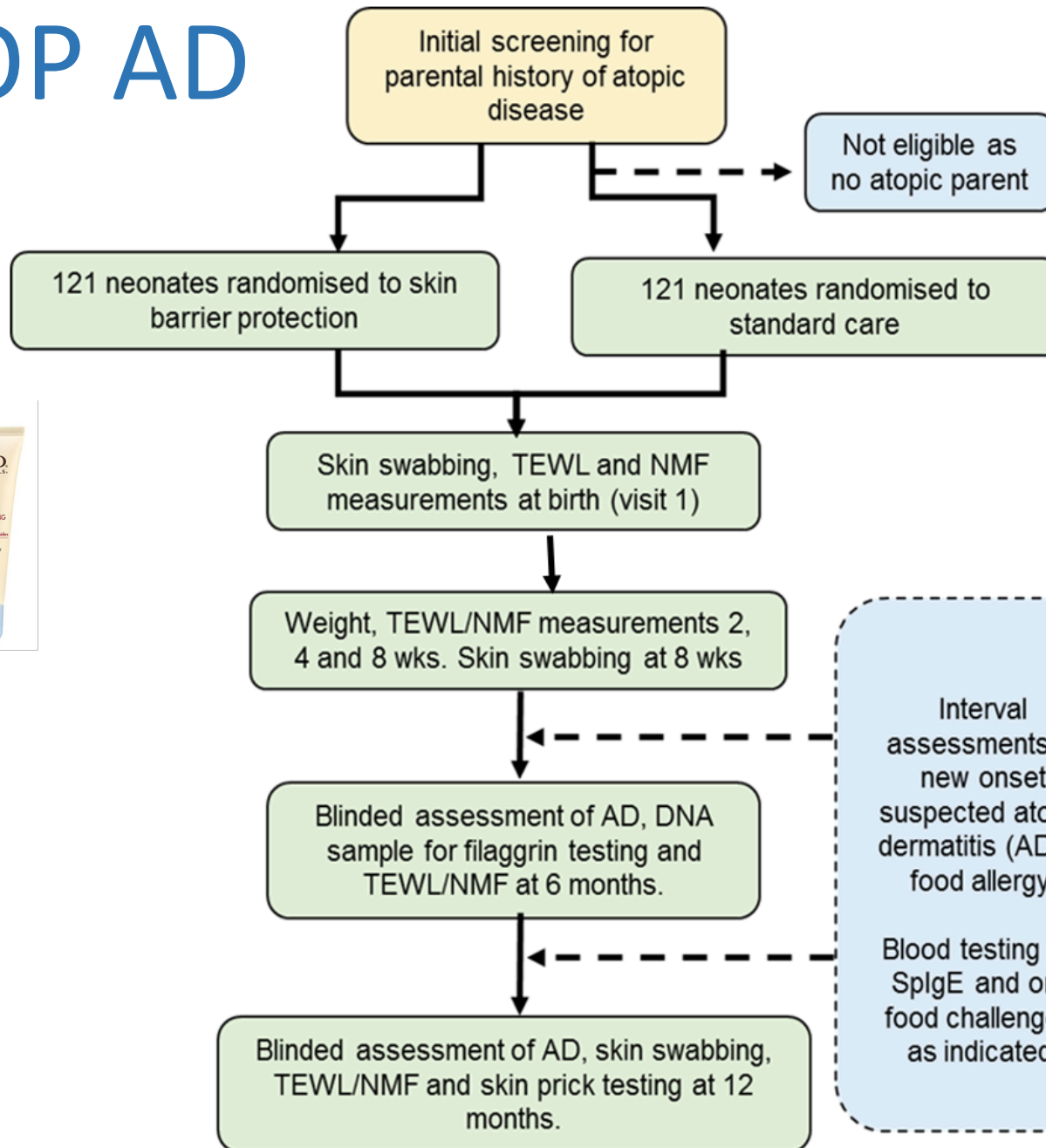


Short-term Topical Application to Prevent Atopic Dermatitis – STOP AD

To investigate if daily emollient use from Birth to 8 weeks can reduce the incidence of AD in High Risk infants.



The STOP AD Study



Recruitment:
High Risk Infants

Randomization:
Twice daily emollient application from 0-8 weeks

Primary Outcome:
Cumulative AD at 12 months

Secondary Outcomes:

- AD at 6 months
- Food Allergy at 12 months
- NMF and TEWL evolution (0-12m)

Interval assessments of new onset suspected atopic dermatitis (AD) & food allergy.
Blood testing for SptgE and oral food challenges, as indicated.



THE LANCET

2020

The Barrier Enhancement for Eczema Prevention (BEEP) trial¹, daily emollient use birth to 12 months, 1394 high-risk infants

“No evidence that daily emollient during the first year of life prevents eczema in high-risk children”

Preventing Atopic Dermatitis and Allergies in Childhood (PreventADALL)², short baths with emulsified oil and cream applied to face on at least 4 days per week from 2 weeks to 8 months, 1171 infants

“Our study does not support the use of these interventions to prevent atopic dermatitis by 12 months of age in infants”

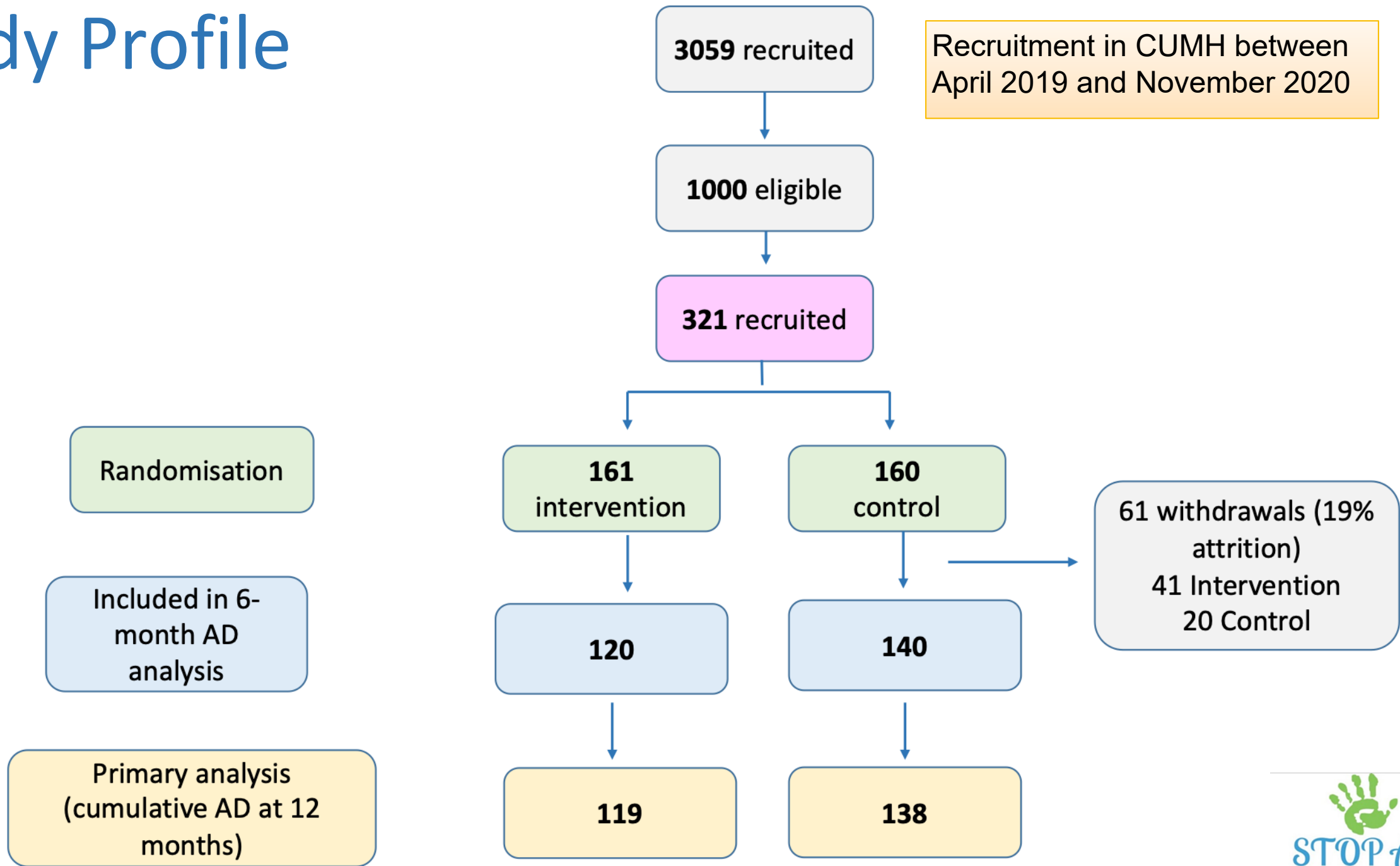
1. Chalmers et al. Lancet Lond Engl. 2020, 21;395(10228):962–72.
2. Skjerven et al. Lancet Lond Engl. 2020 Mar, 21;395(10228):951–61.

Study/Characteristics:	PreventADALL	BEEP	STOPAD
Recruitment Criteria	Parent with atopic history	Parent Reported AD, AR. Or, AA diagnosed by doctor	Parent with atopic history
Type of Intervention(s)	Bath additive and facial moisturizer/ cream Early complementary feeding, or both	Emollient	Emollient and early complementary feeding advice
Type of Moisturizer	Paraffinum liquid and trilaureth-4-phosphate and Ceridal	Diprobace cream or Doublebase Gel	Ceramide dominant emollient
Duration of Intervention	8 months	12 months	2 months
Application rate	At least 5 days per week	Regularly (once or twice daily)	Twice daily
Onset of treatment	Beginning at 2wk of life	At a maximum of 21 days after delivery	From birth
Examiner	Blinded	Blinded	Blinded

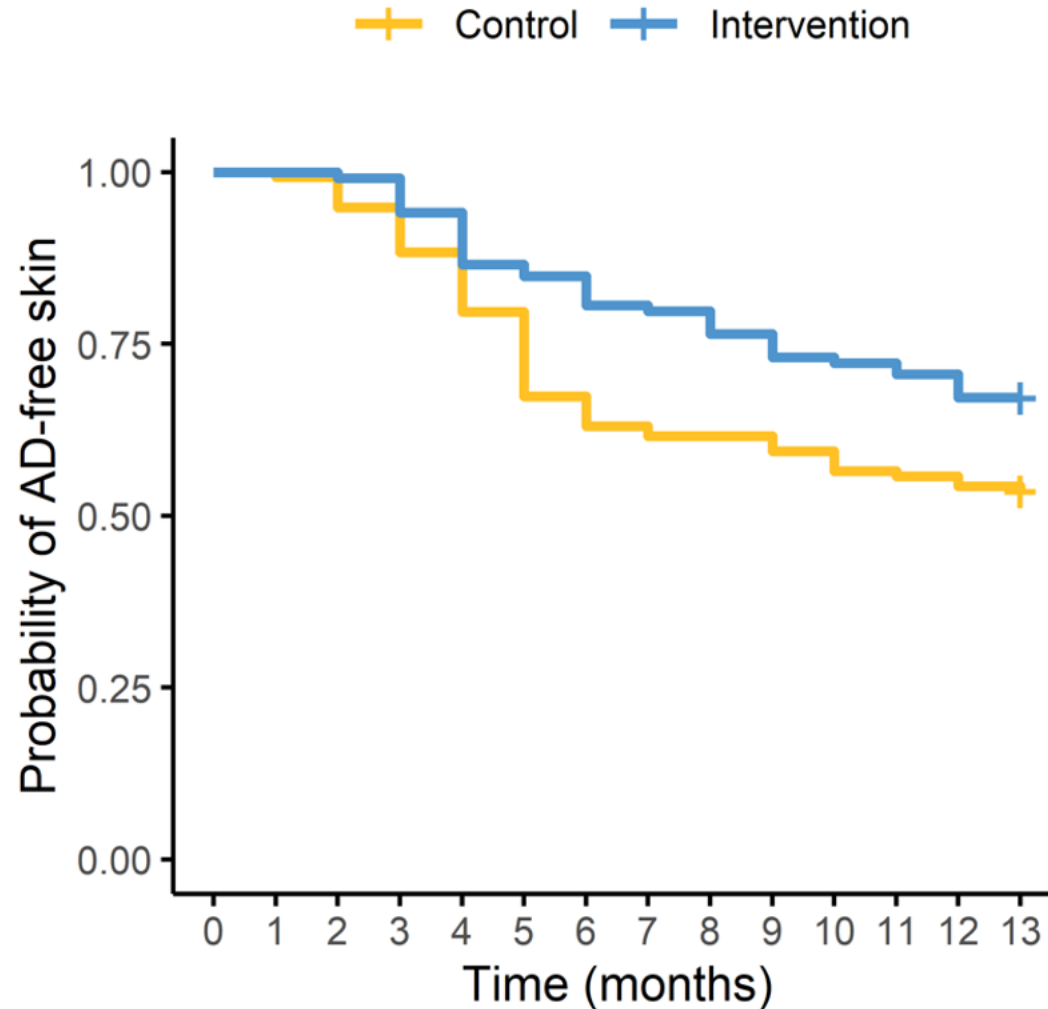


Infant

Study Profile



Kaplan Meyer - time to treat analysis



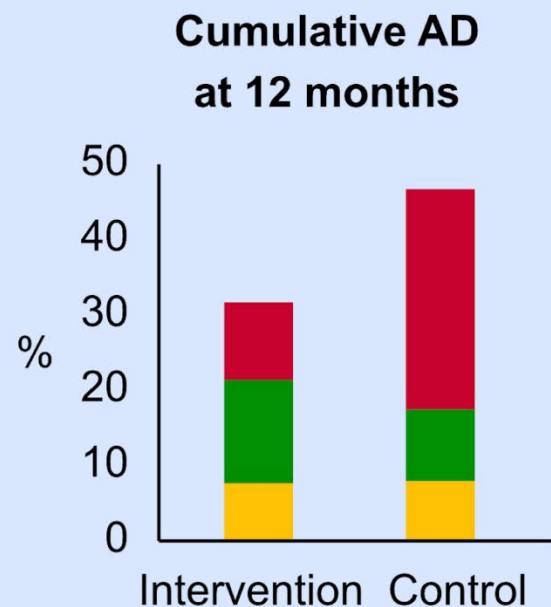
$P = 0.016$, log-rank test

Study design



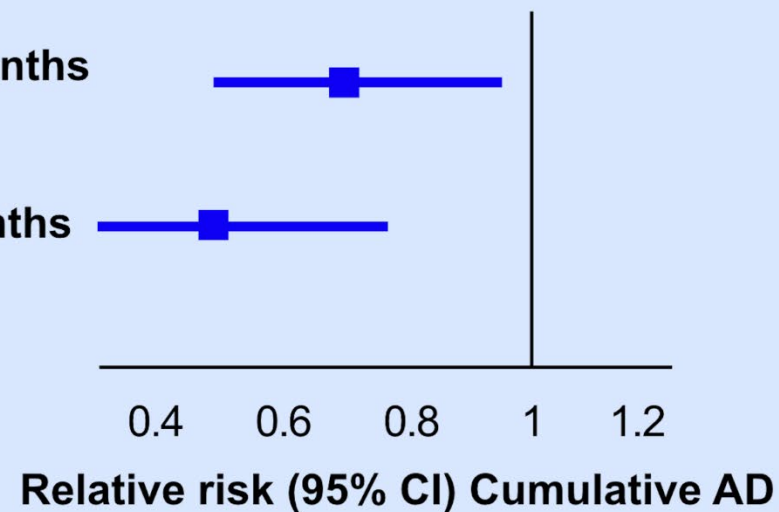
Age AD onset

- Persistent (6 & 12 months)
- > 6 months
- ≤6 months with remission



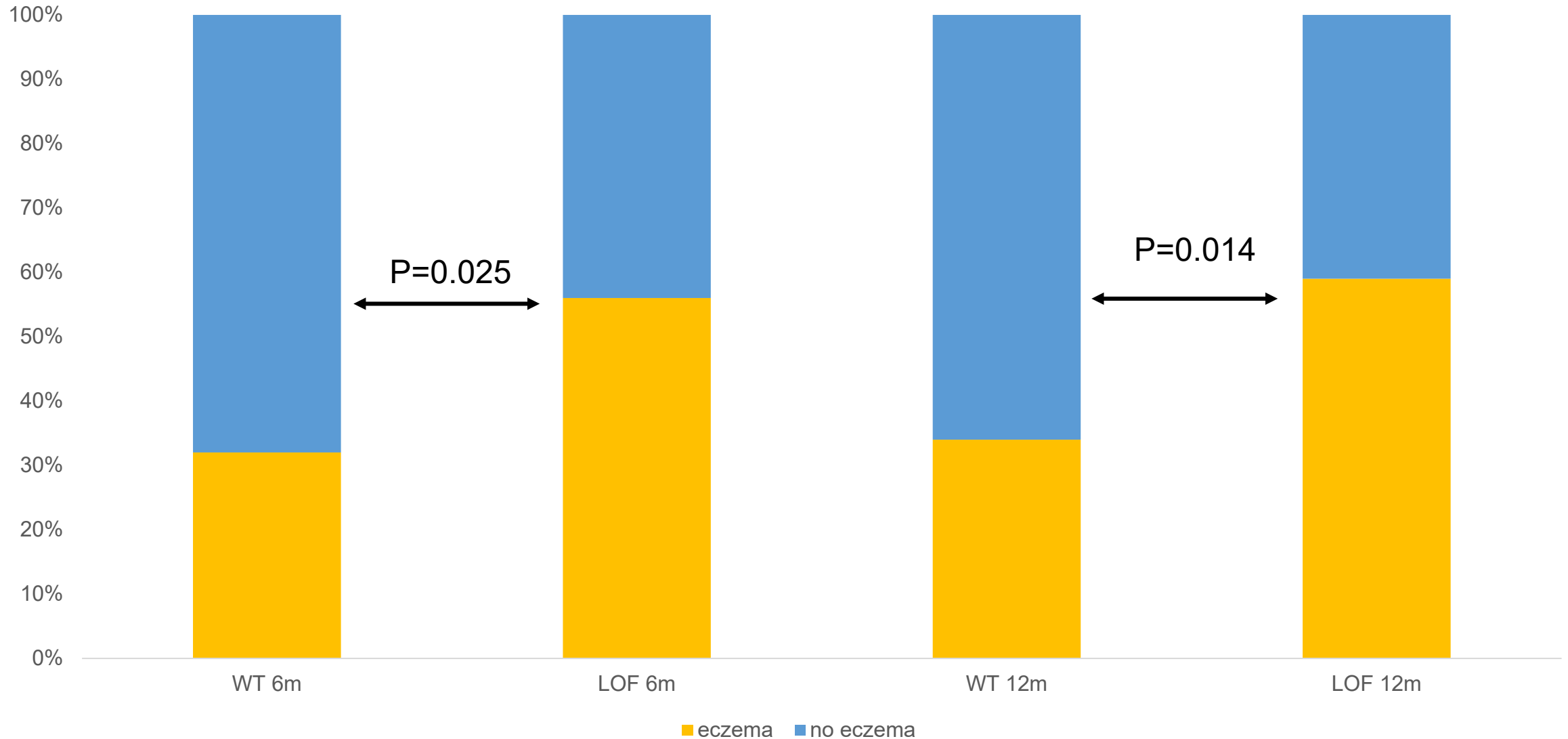
12 months

6 months

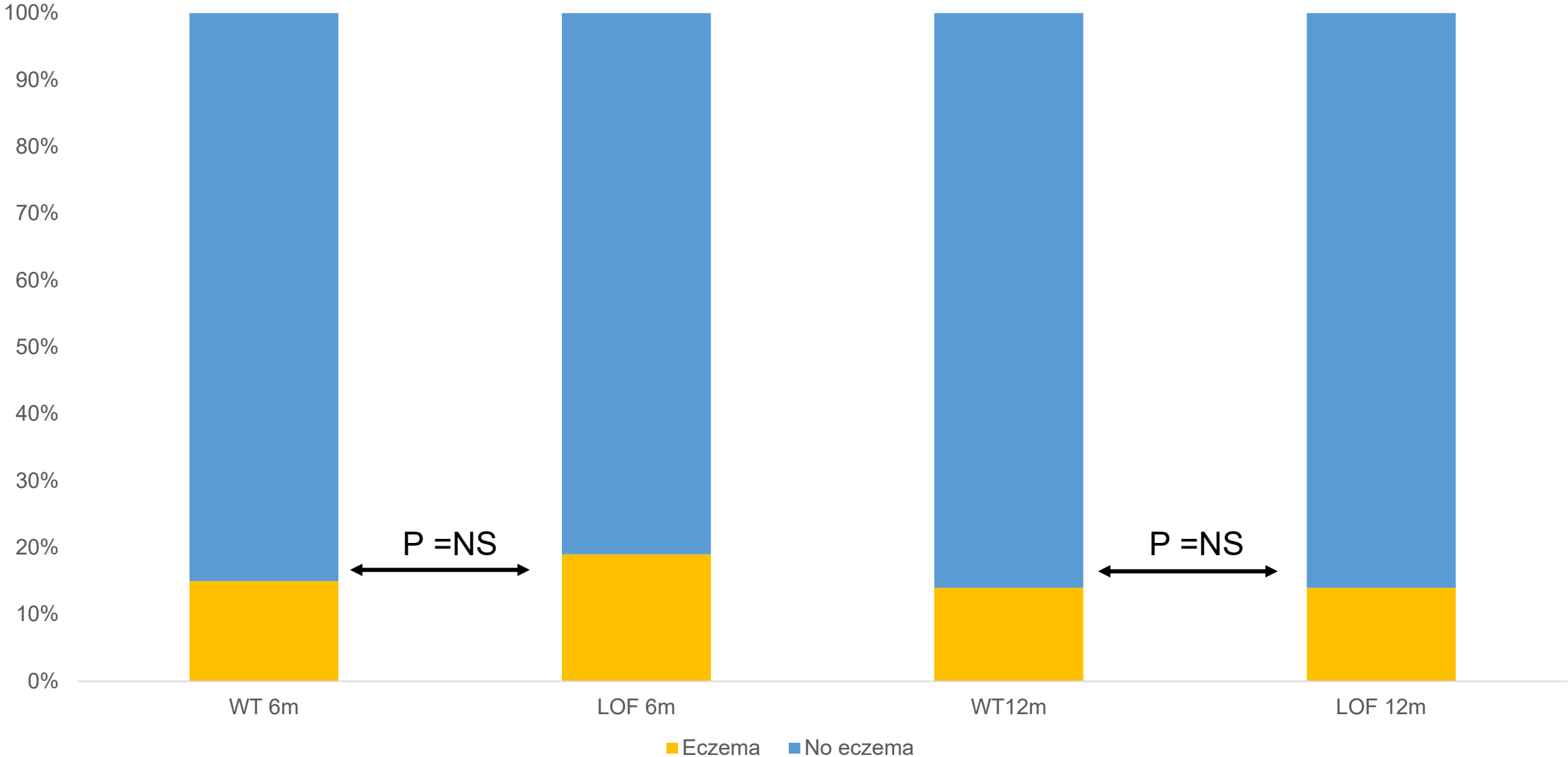


Short-term emollient use in the neonatal period associated with ↓ AD incidence in the first year

In control group higher eczema rate in LOF-FLG (n=23) than WT-FLG (113) @6 and 12m



In intervention group same eczema rate in LOF-FLG (n=21) than WT-FLG (98) @6 and 12m



Baseline Characteristics

Balanced across the groups

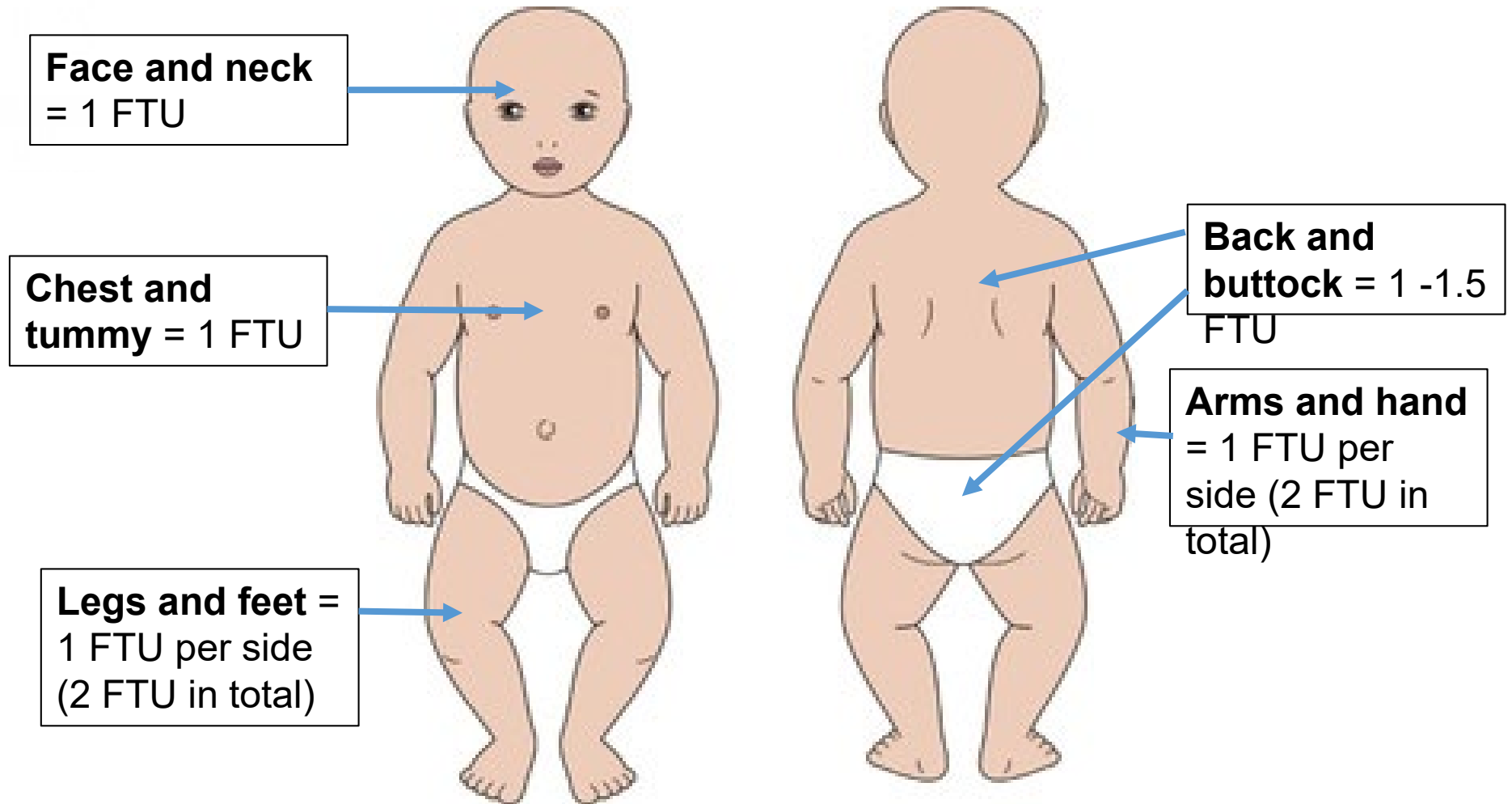
	Intervention (n = 161), n (%)	Control (n = 160), n (%)
Maternal characteristics		
Age [mean (SD) years]	33.3 (4.4)	34.1 (4.8)
Country of birth (Ireland)	142 (88.2)	139 (86.9)
Ethnicity (white)	156 (96.9)	158 (98.8)
Infant characteristics		
Sex (male)	79 (49.1)	85 (53.1)
Gestational age [mean (SD) weeks]	39.7 (1.1)	39.5 (1.1)
Mode of delivery (vaginal)	98 (61.3)	103 (64.4)
Age randomised [mean (SD) days]	1.9 (1.0)	1.8 (0.8)
FLG genotyping		
FLG wildtype	96/117 (82.1)	113/136 (83.1)
FLG null mutation (one)	21/117 (17.9)	22/136 (16.2)
FLG null mutation (two)	0	1/136 (0.7)

Very little product used, like steroids = parent friendly

1 Finger tip unit



1 finger tip unit
(FTU) = 0.5 g
2 FTU = 1 g



Adherence to Study Protocol - Questionnaire Data

	Control (n = 141)			Intervention (n = 121)		
	2 weeks (n = 137)	4 weeks (n = 137)	8 weeks (n = 141)	2 weeks (n = 118)	4 weeks (n = 120)	8 weeks (n = 119)
Never	47 (34.3)	39 (28.5)	34 (24.1)	0	0	0
Occasionally	25 (18.2)	25 (18.2)	25 (17.7)	1 (0.8)	0	0
Once/week	7 (5.1)	9 (6.6)	10 (13.5)	1 (0.8)	0	2 (1.7)
2-3/week	32 (23.4)	40 (29.2)	44 (31.2)	3 (2.5)	3 (2.5)	5 (4.2)
4-6/week	16 (11.7)	17 (12.4)	11 (7.8)	8 (6.8)	6 (5.0)	9 (7.6)
Daily*	10 (7.3)	7 (5.1)	8 (5.7)	105 (89.0)	111 (91.7)	103 (86.6)
*Twice/day	2 (1.5)	0	0	75 (63.6)	83 (69.2)	87 (73.1)

Intervention: 89 (78.1%) reported daily emollient use at all three time-points.

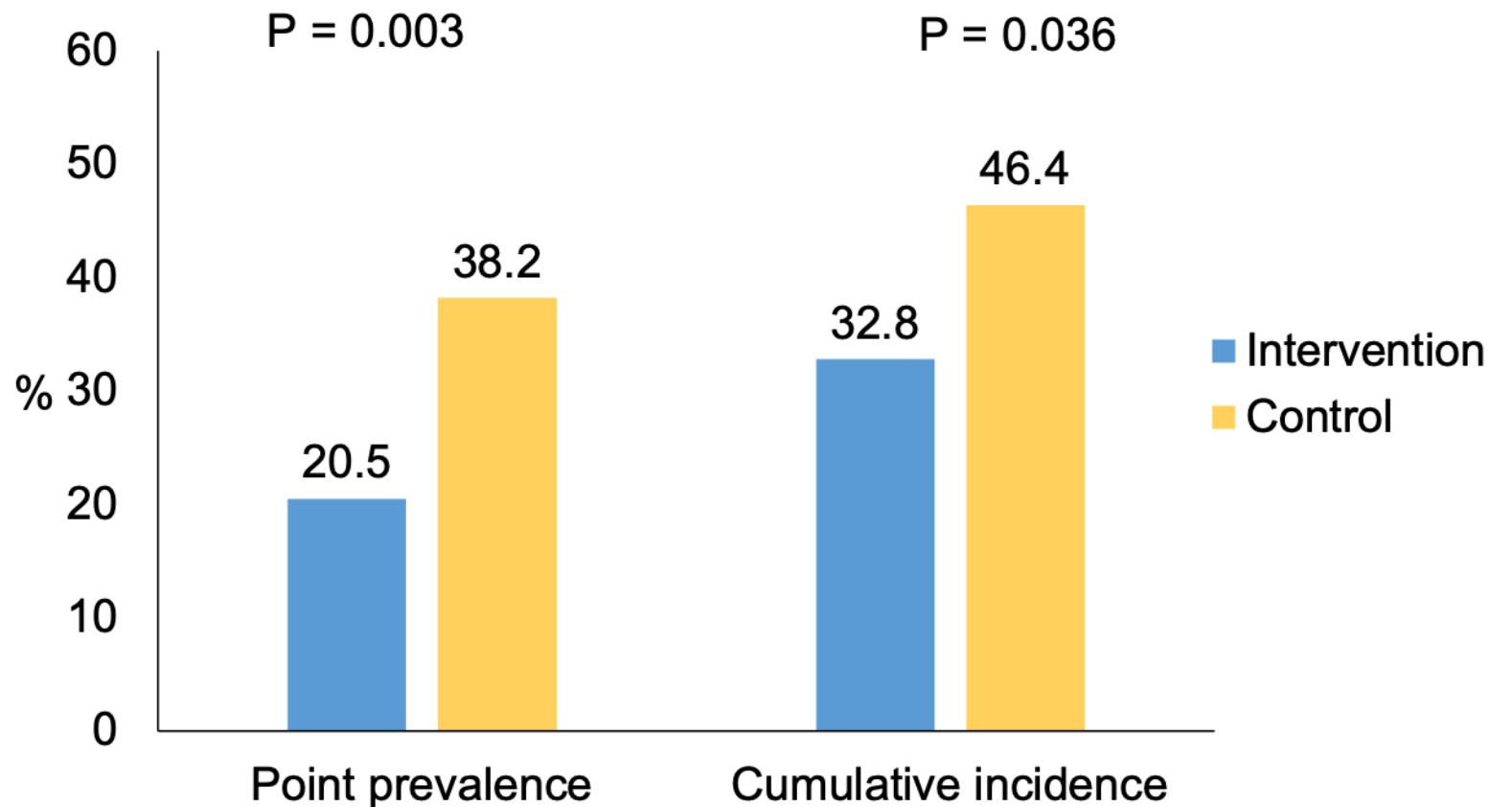
Control: 90 (68.2%) reported using emollients on less than 4 days per week at all three time-points.

AD at 12 months

Daily emollient use associated with a **29%** reduced risk of cumulative AD at 12 months

RR (95% CI): 0.536
(0.354, 0.813)

RR (95% CI): 0.707
(0.516, 0.967)



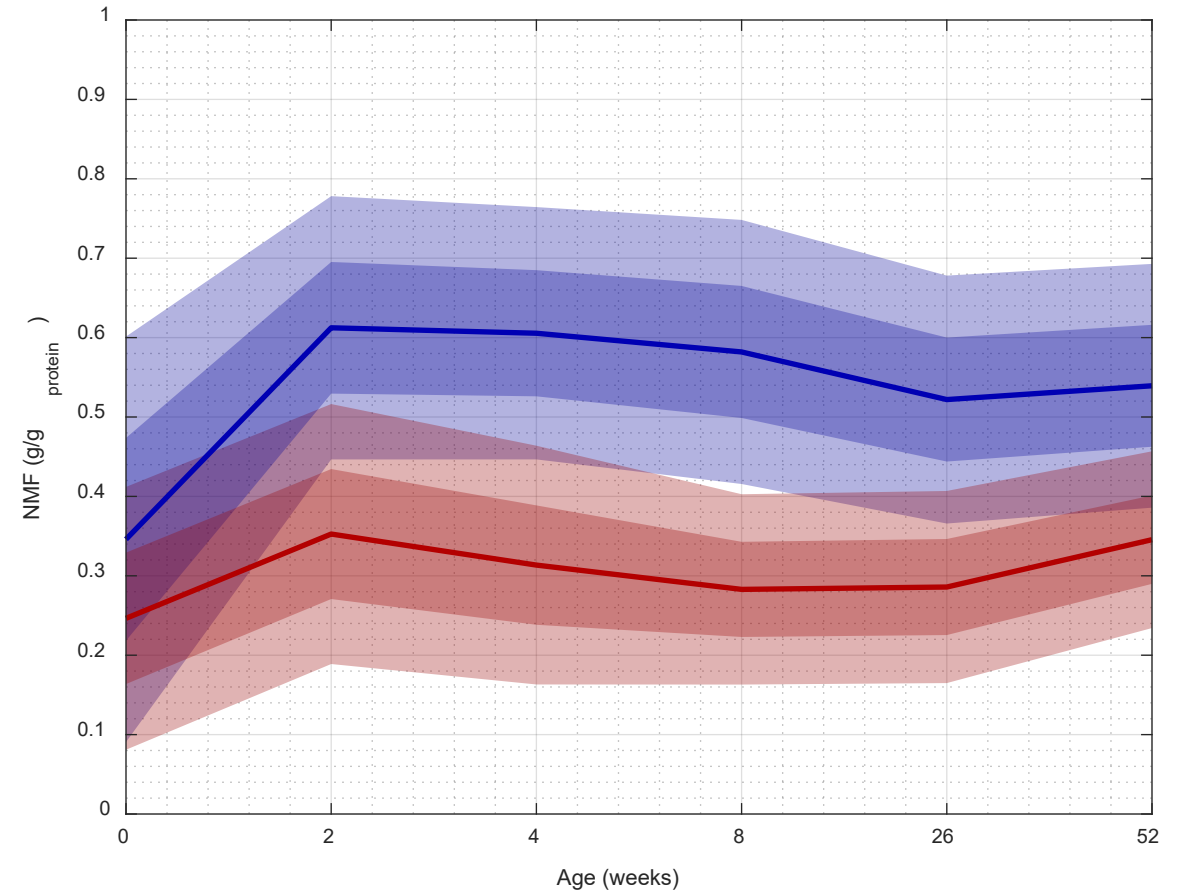
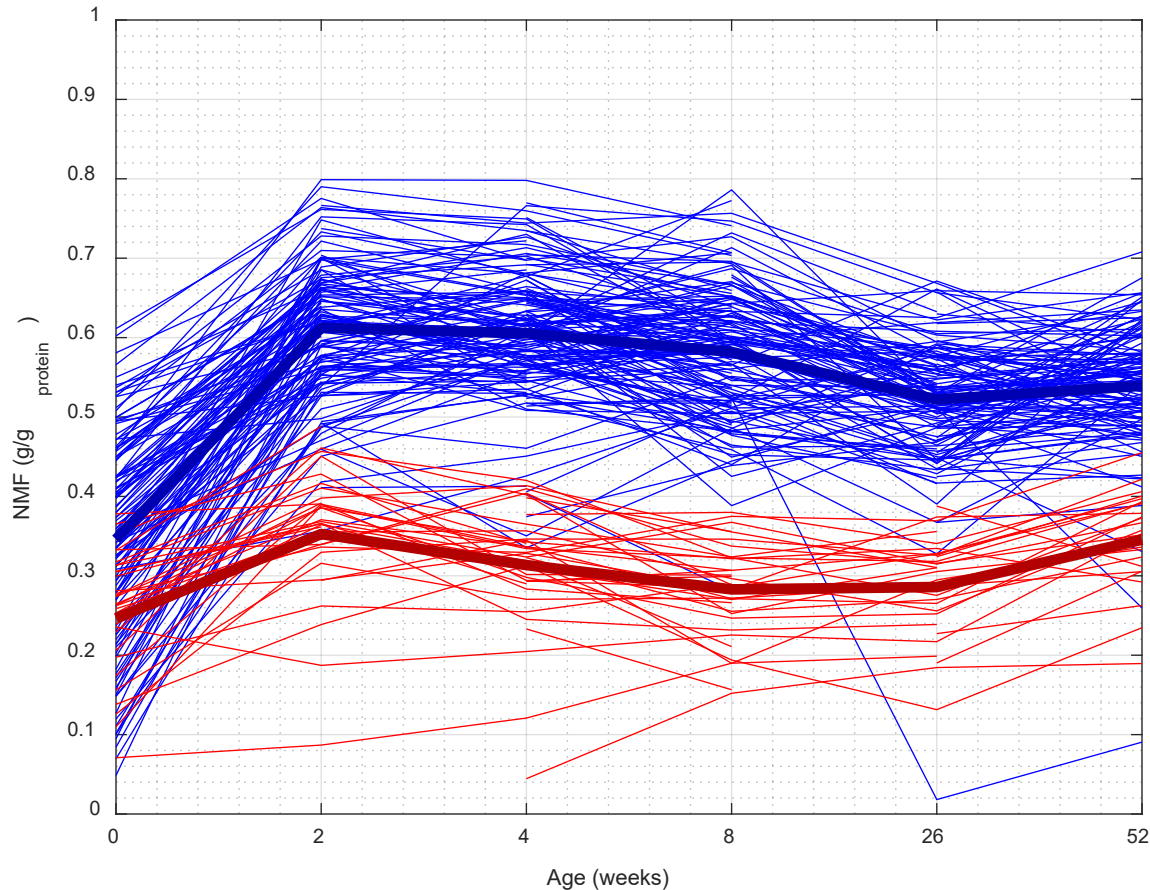
NMF increases from birth to 2 weeks with divergence according to FLG status

FLG-wt ■ FLG -m ■

Each point of the curve is the average for a subject. Each curve is a subject.

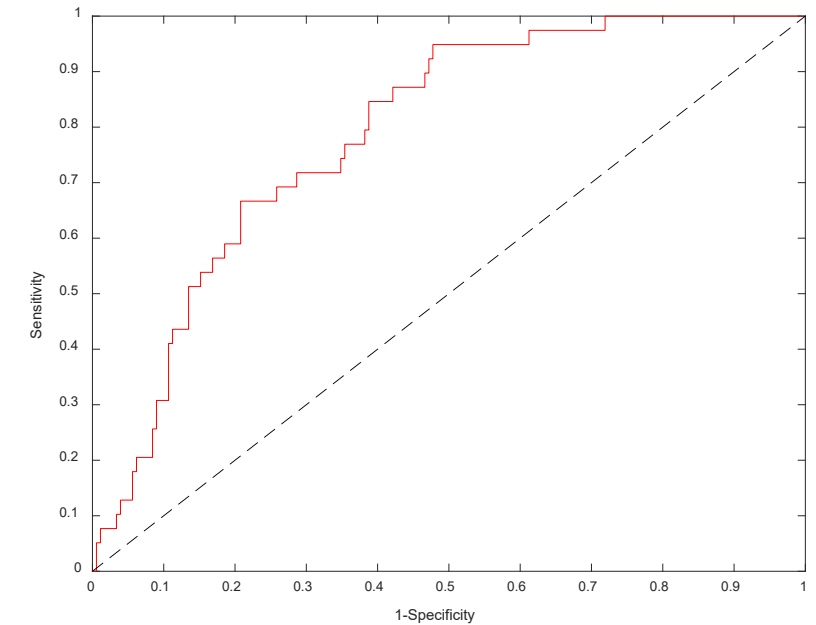
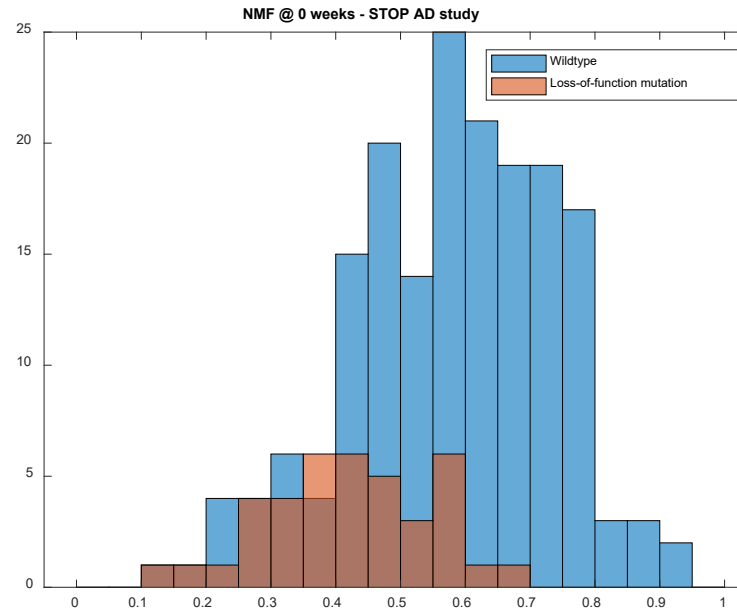
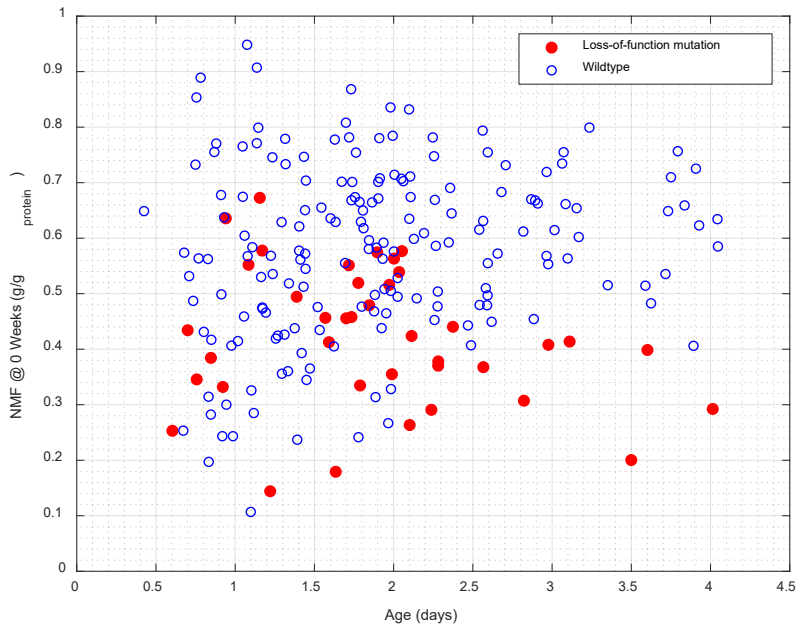
Thick lines are the average

Same as the graph on the left, but representing only the average, the area of 1xSTD (dark shade) and area of 2xSTD (lighter shade)



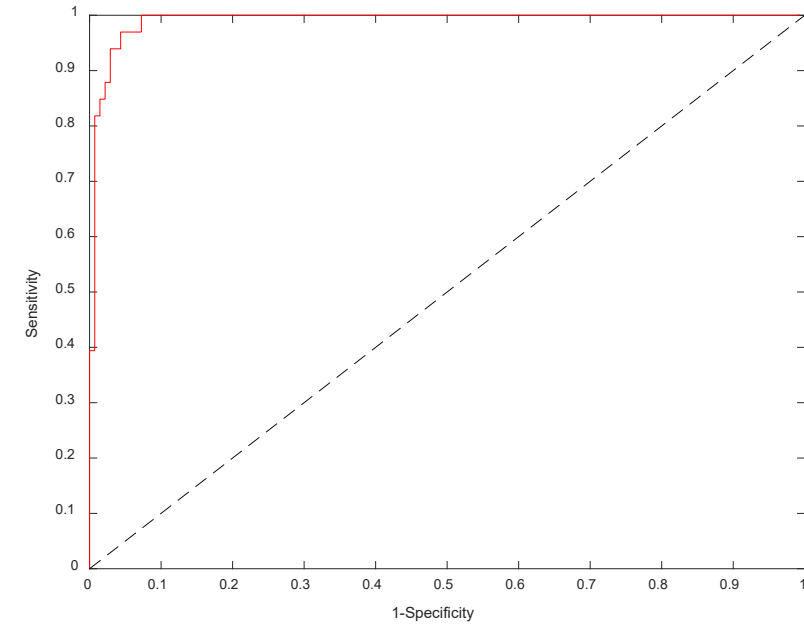
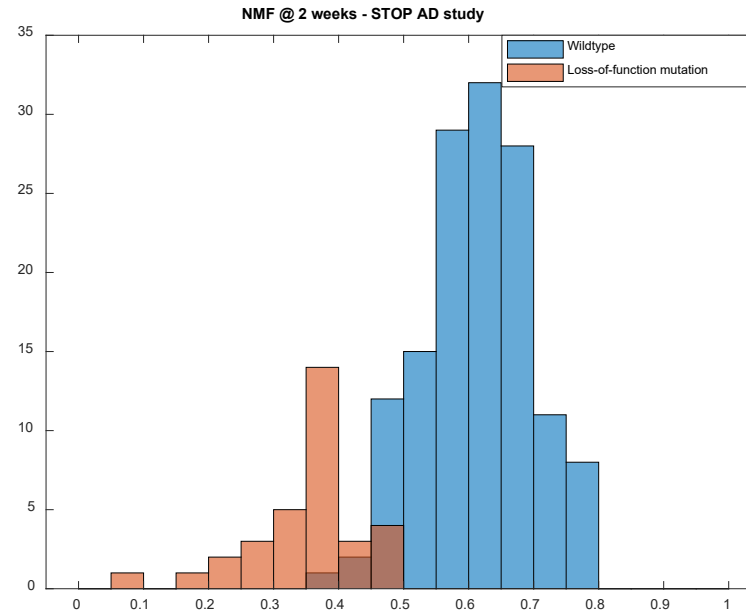
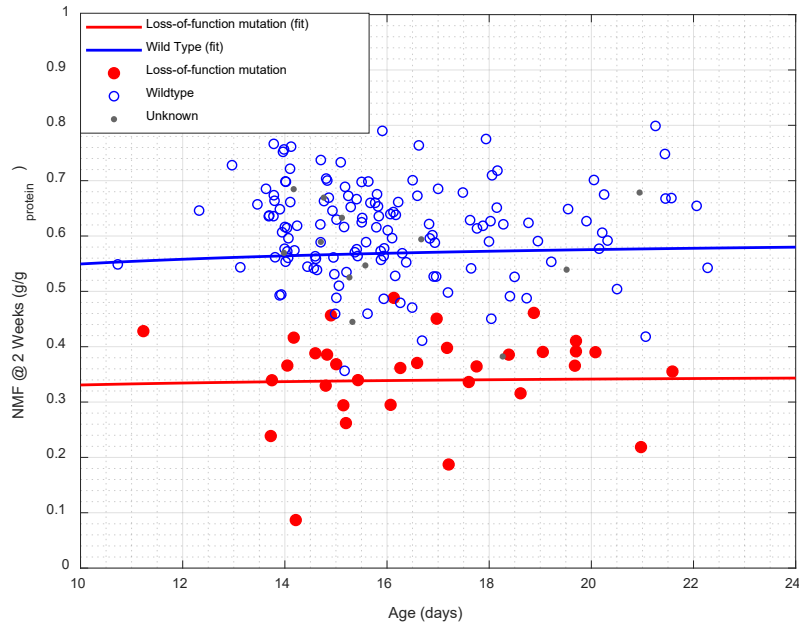
NMF at birth, corrected for build up rate using the fitted curve

Optimal threshold: 0.581, Sensitivity: 0.949, Specificity: 0.522



We can set a threshold at birth above which subjects don't need to be followed up due to lower risk. Subjects below threshold are at a high risk of being a FLG mutation carriers and can be advised to be measured at 2 weeks.

NMF threshold of 0.49 at 2 weeks is 100% sensitive, 92% specific for FLG status



At 2 weeks, we can tell with a high degree of certainty who carries a mutation. Clinical advice is adapted based on this measurement.

Short-term Topical Application to Prevent Atopic Dermatitis – STOP AD

To investigate if daily emollient use from Birth to 8 weeks can reduce the incidence of AD in High Risk infants.

The incidence of AD at 12 m was **significantly** decreased by early short-term application of a readily available ceramide based emollient, when applied from birth to 8 weeks, suggesting a viable therapeutic model for a risk reduction of AD in infancy.

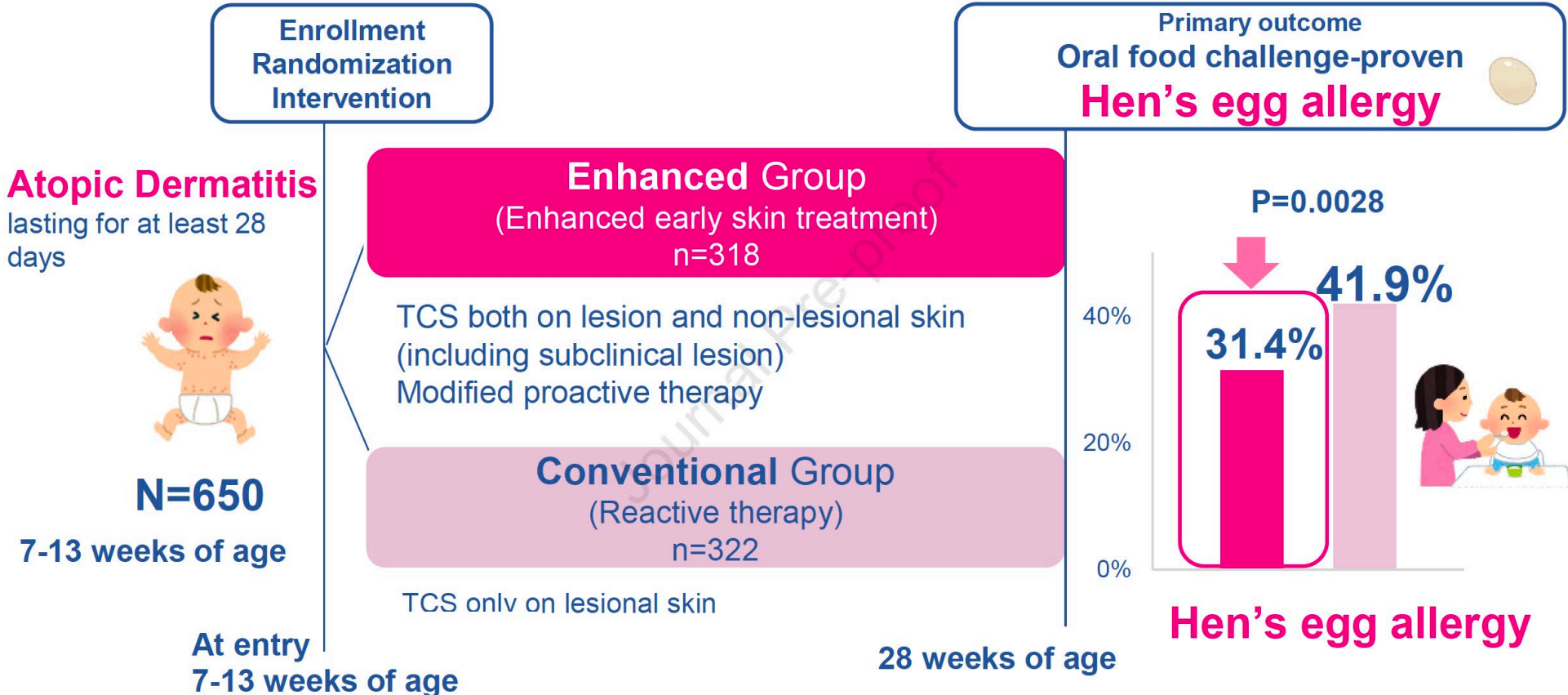


Early aggressive AD care decreases incidence of egg allergy.. at a cost



Enhanced early skin treatment for atopic dermatitis in infants reduces food allergy

Journal Pre-proof



Abbreviations
PACI: Prevention of Allergy via Cutaneous Intervention
TCS: Topical corticosteroids

Safety Issue
Enhanced treatment lowered body weight and height at 28 weeks of age.



Discussion

- Just the luck of the Irish?
- Timing? Goldilocks effect
- Product ? Single active ingredient or the right combination
- Dosing? literally very light touch, using fingertip unit, only for 8 weeks
- Safety? Very safe
- Feasibility?
 - Low recruitment rate
 - For selected high risk babies like these or general population?
- Needs replication in other populations/durations/ products

Acknowledgements

Study team

PIs: Profs Jonathan Hourihane, Alan Irvine and Deirdre Murray

Fellow Dr Dhanis Lad

Project managers: Dr. Carol Ní Chaiomh, Darina Sheehan

Study nurses: Ita Herlihy, Geraldine Roche, Claire O' Halloran, Laura Lee

Special thank you to:

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Stop AD study

D Lad, C Ni Chaoimh, D Sheehan, A Irvine



Sláinte Leanaí Éireann



Children's Health Ireland

CHI and HSE Allergy

A Byrne, M Kelleher, F Heraghty, N Flynn

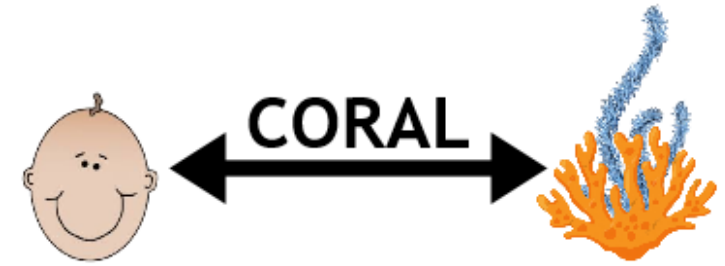
Inter alia

Y d'Art, M Greenhawt



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CORAL study

R Franklin, J Lennon, N McCallion



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