Micronutrient-transport by whey proteins: A missing link to health and immune resilience.

Priv.Doz. Dr. Franziska Roth-Walter

13th FACE Conference "Roh - Cru - Raw”, Grangeneuve-Fribourg, Swit

Session 3: Health effects, October 13, 2023

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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	University of Veterinary Medicine Vienna
Research Grant (P.I., collaborator or consultant; pending and received grants)	Biomedical International R+D, Vienna, Austria 2019-2020
Other research support	Bencard Allergie GmbH grant award 2018, Austrian Science Fund FWF Biomedical International R+D grant 2019, European Society of Veterinary Dermatology
Speakers Bureau / Honoraria	FOMF, VAEM, Bencard Allergie GmbH, Munich, Germany and Vienna, Austria, and Allergy Therapeutics, Worthing, UK, Springer Medizin HNO, Lofarma
Ownership interest (stock, stock-options, patent or intellectual property	Lead inventor of EP2894478 (Roth-Walter F et al. Method and means for diagnosing and treating allergy), Founder of ViaLym
Consultant / advisory board	Biomedical International R+D GmbH, Vienna, Austria (2018-2021)

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 (e.g., owning stocks of a related company, having received honoraria, consultancy fees), research interests (research support by grants or otherwise), organisational interests and gifts.

Micronutritional deficiencies: absolute and functional

Iron 

Vitamin A 

Absolute – extreme form

- no iron → anaemia
- no Vitamin A → night blindness/xerophtalmia

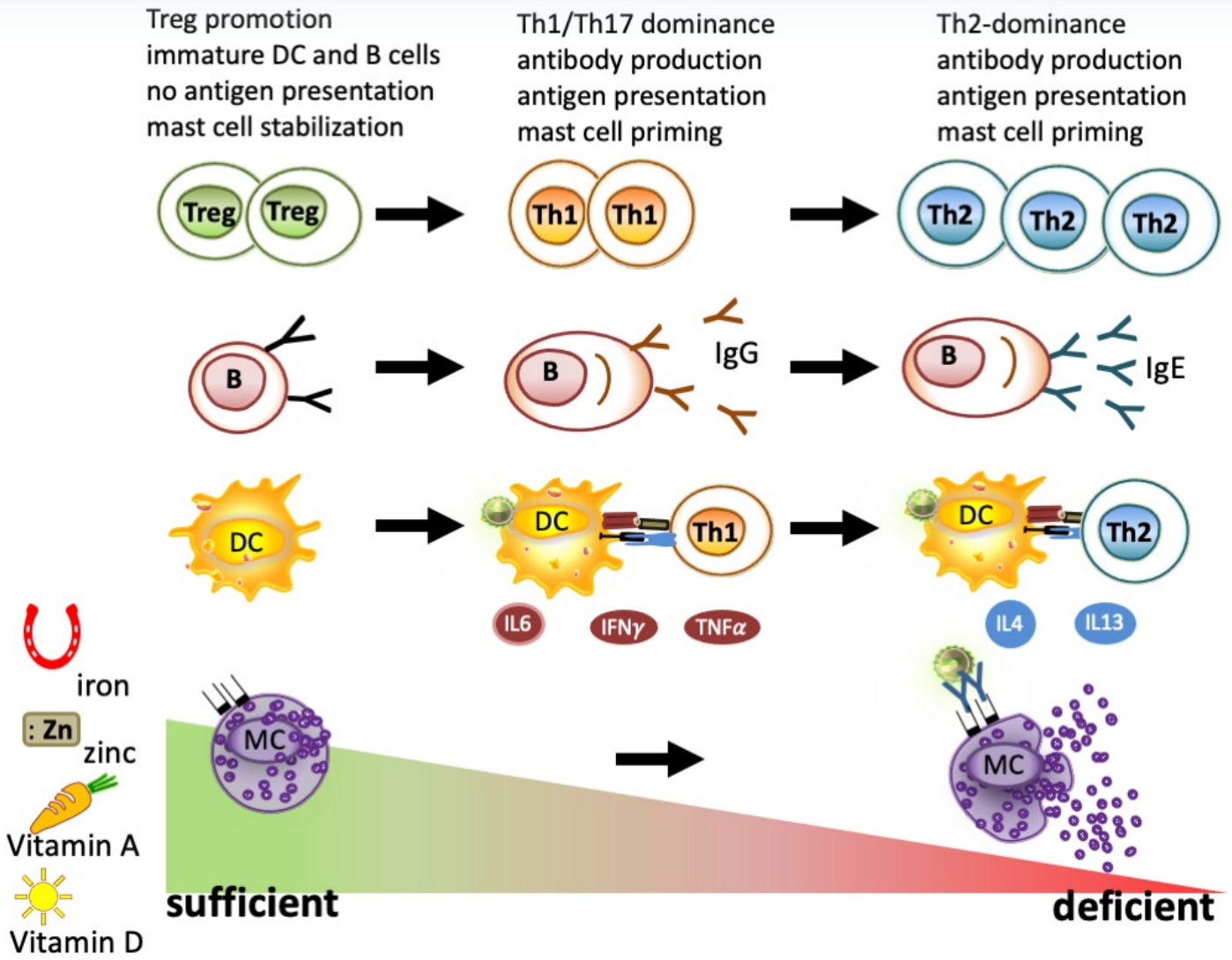
Functional – not accessible

- iron → inflammation
- Vitamin A → inflammation

Iron- and Vitamin A- deficiencies are associated with increased all-cause morbidity and mortality

Front Nutr . 2023 Mar 16;10:1096288
Clin Exp Allergy . 2017 Jun;47(6):751-759.

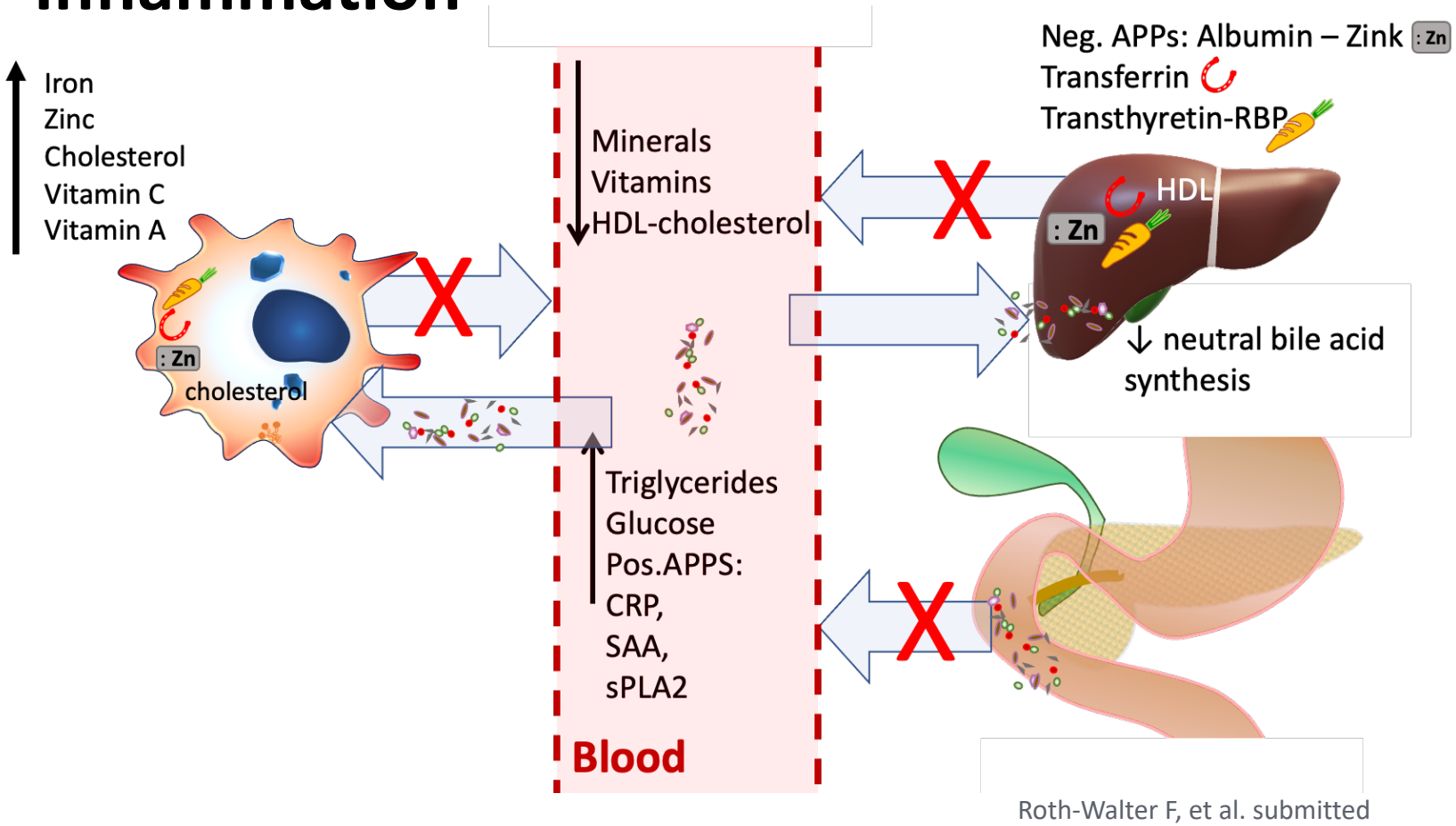
Nutritional immunity: deficiencies as trigger for inflammation



Front Allergy. 2022 May 10;3:859922.
Blood. 2010 May 6;115(18):3810-6
Adv Nutr. 2017 Mar 15;8(2):197-212.
J Lab Physicians. 2021 Dec 31;14(2):190-196

Disturbed nutrient homeostasis during inflammation

Inflammation



Roth-Walter F, et al. submitted

Decreased

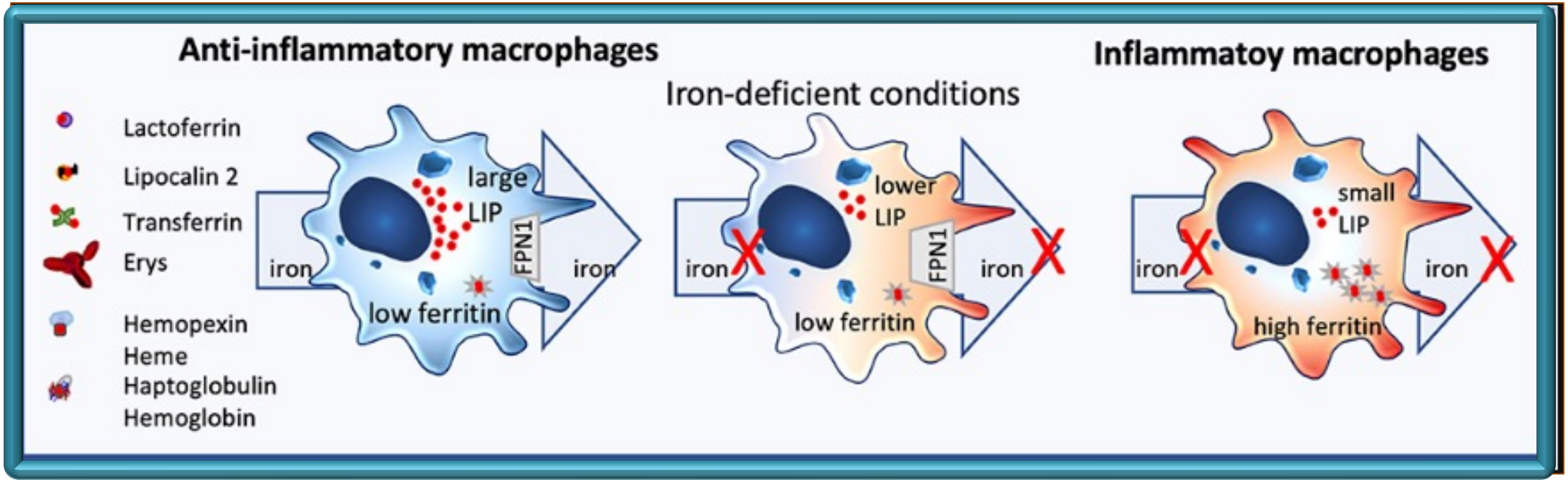
- minerals and vitamins, HDL-cholesterol
- nutrient-associated proteins: transferrin, albumin, transthyretin

Increased

- triglycerides and glucose
- positive acute phase proteins:
  - serum amyloid A SAA
  - C-reactive protein CRP
  - Lipopolysaccharide binding protein LBP

Mil Med Res. 2022 Jan 20;9(1):4; J Lipid Res. 2004 Jul;45(7):1169-96; Curr Opin Lipidol. 2016 Oct;27(5):521-30; Science. 2021 Jul 23;373(6553):eabe6729, Front Endocrinol (Lausanne). 2019 Jul 10;10:470.; J Clin Med . 2020 Feb 17;9(2):547

Mimicking infections with iron deficiency



Front Allergy. 2022 May 10;3:859922

Anemia of chronic inflammation

Functional micronutritional deficiencies affects many patient groups

Atopic diseases

Cancer

Autoimmune diseases

Adipositas

Worsened Outcome
Worsened Prognosis

Chronic Kidney diseases

Chronic pulmonary diseases

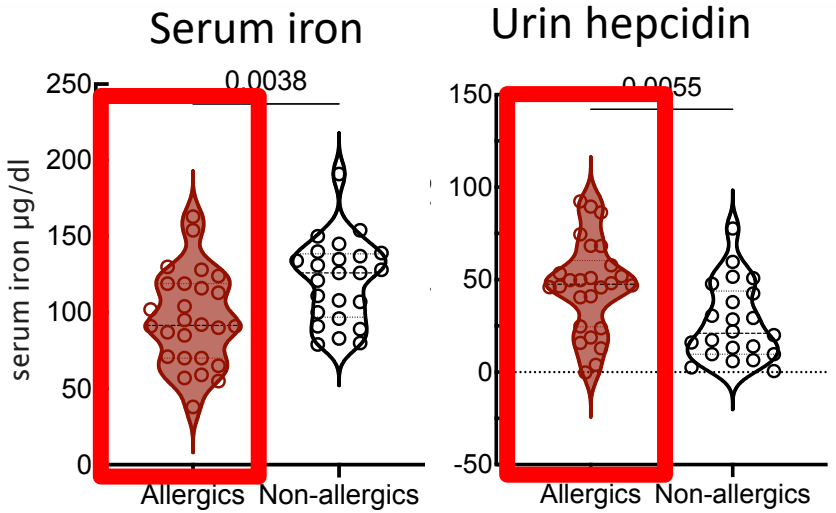
Congestive heart failure

Inflammatory bowel disease

→ Alternative strategies for dietary micronutritional uptake necessary

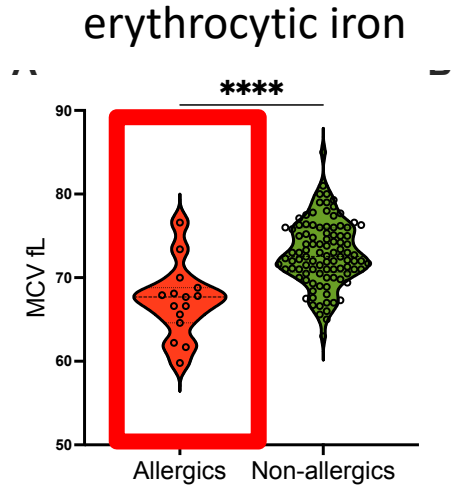
. JCI Insight 2020; 5; Haematologica 2010; 95:1814-22.; Petje LM, et al. Allergy 2021. Luo J, et al Front Endocrinol 2021; 12:629831.; Chang Ret al. Curr Med Res Opin 2020; 36:985-92.Drury KE, et al. JAMA Pediatr 2016; 170:29-34.; Rhew K, et al. BMC Pediatr 2019; 19:455.; Rhew K, et al. Int J Environ Res Public Health 2020; 17.; Krishna MT, et al. Eur Respir J 2019; 54.; Susantitaphong P, et al. . Am J Nephrol 2014; 39:130-41; Albaramki J, et al. Cochrane Database Syst Rev 2012; 1:CD007857.; Reinhold J, , et al. Int J Cardiol 2021; 328:46-54.; Osman M, , et al. Am J Cardiol 2021; 141:152-3.; Zhang J, et al. . Postgrad Med J 2020; 96:766-76.;Nickol AH, , et al. . BMJ Open 2015; 5:e007911. Cloonan SM, et al. . Am J Respir Crit Care Med 2017; 196:1103-12; Pizzini A, et al. Int J Med Sci 2020; 17:2232-9.; Teng IC, et al. Obes Rev 2020; 21:e13080.; Zhao L, et al. Obes Rev 2015; 16:1081-93.

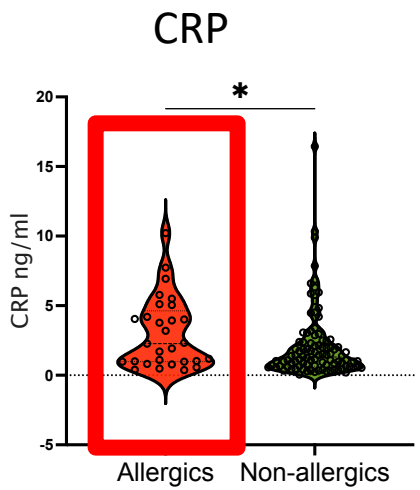
Functional iron-deficiency in atopic diseases



non-anemic women with allergic rhinits

Petje LM et al. Allergy. 2021 Sep;76(9):2882-2886

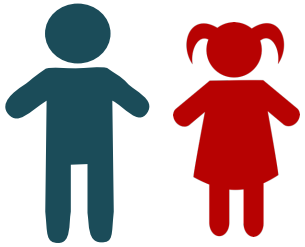


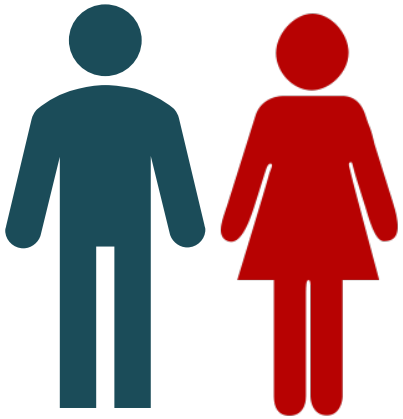


dogs with atopic dermatitis

Frizzos-Ramos C et al. submitted

Atopy and micronutritional deficiencies





Maternal iron supplementation

0.2 OR for atopic dermatitis
0.58 OR for asthma
0.33 OR when mother asthmatic

6-8 x anemia

3.5 x 1.6x anemia

Any allergy at 2 years

1.80 OR anemia at age 3

Asthma

HR 4.6 Anemia incidence

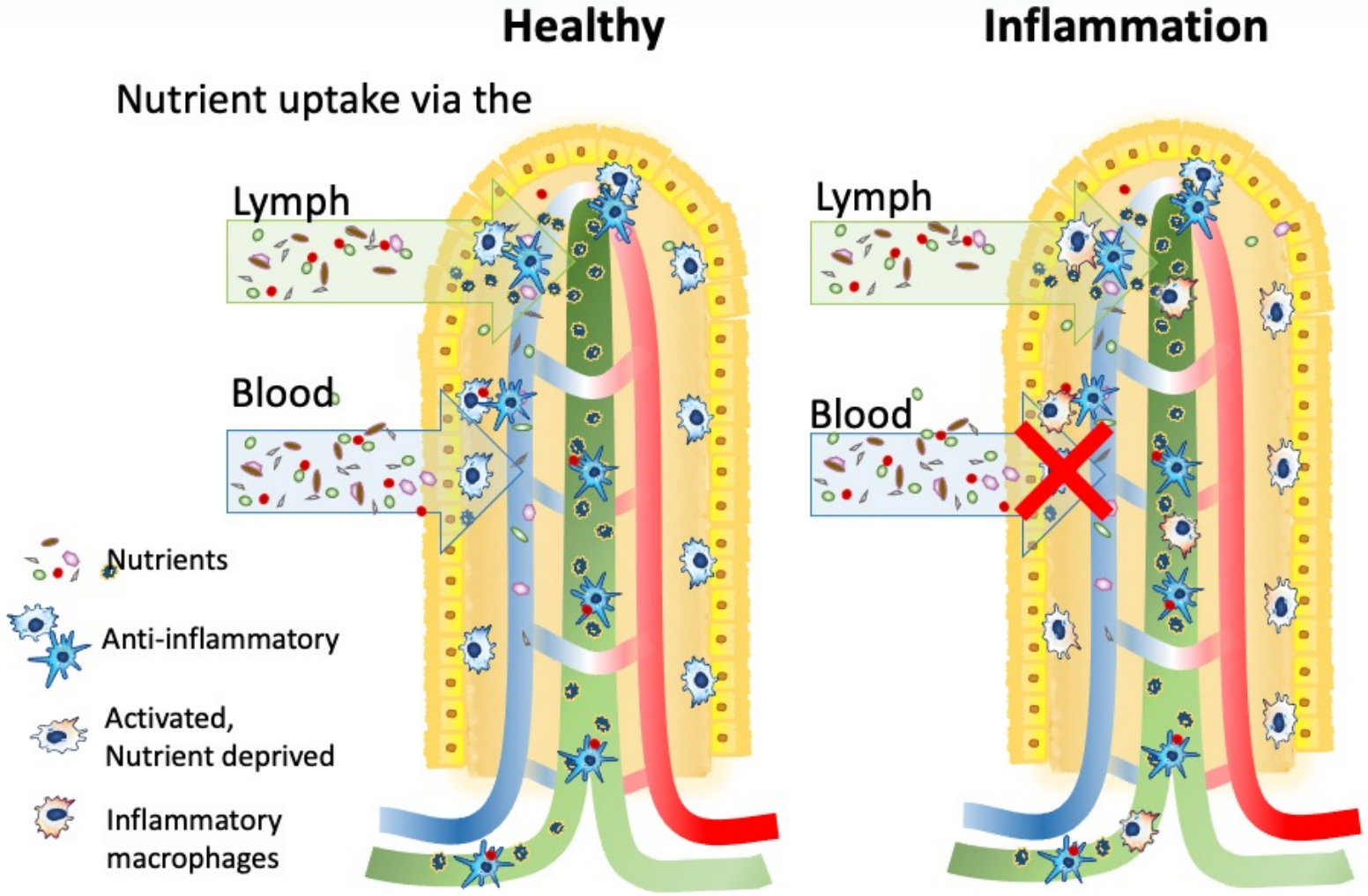
Clin Epidemiol. 2023 Jan 5;15:31-38., Nutrients. 2022 Oct 17;14(20):4335.; Ann Allergy Asthma Immunol. 2021 Jul;127(1):57-63 ; Pediatr Pulmonol. 2021 Jun;56(6):1771-1778; Eur Respir J. 2020 Jun 4;55(6):1902335; Int J Environ Res Public Health. 2020 Mar; 17(6): 1978; Arch Dermatol Res. 2019 Jul;311(5):361-367; BMC Pediatr. 2019 Nov 25;19(1):455; BMJ Open Respir Res. 2018 Mar 30;5(1):e000275; J Obstet Gynaecol Res. 2018 Apr;44(4):614-622; Clin Exp Allergy. 2017 Dec;47(12):1615-1624; JAMA Pediatr. 2016;170(1):29-34; Br J Nutr. 2014 Dec 28;112(12):2018-27; Eur J Clin Nutr. 2010 Mar;64(3):245-52.; Eur Respir J. 2004 Aug;24(2):292-7

Disturbed nutrient homeostasis during inflammation

Inflammation

Blood → Liver
- amino acids
- monosaccharides
- short-chain fatty acids

Lymph → Immune cells
- fat
- fat-soluble vitamins
- Micelles and particulate substances
- innate defense proteins



Roth-Walter F, et al. submitted

Cow milk

- Drinking farm milk protects against atopy and asthma

		hayfever
Nonfarmers *N* = 1146	65 (5.7)	
Raw milk consumed		
Never *n* = 437 (38.1%)	36 (8.2)	1.00 (ref)
Sometimes *n* = 122 (10.6%)	7 (5.7)	0.68 (0.44–0.94)
Regularly *n* = 587 (51.2%)	22 (3.7)	0.45 (0.34–0.54)

Allergy. 2013;68(5):644-50. doi: 10.1111/all.12147

- Whey proteins protects against asthma

α-Lactalbumin (μg/mL)§	704	0.71	(0.52-0.97)*
β-Lactoglobulin (μg/mL)§	713	0.62	(0.39-0.97)*

- Heat abrogates protection

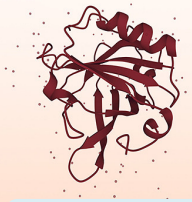
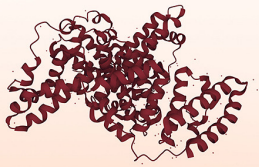
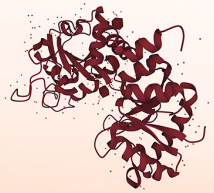
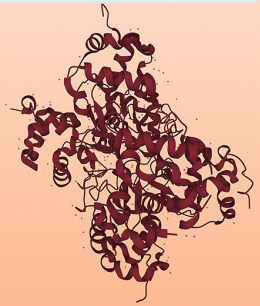
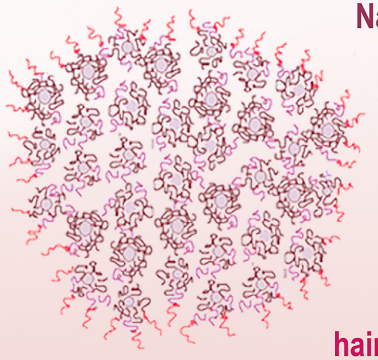
Shop milk: high heat–treated	531	1.00	
Shop milk: pasteurized	52	0.50	(0.22-1.12)
Farm milk: heated	60	0.97	(0.49-1.91)
Farm milk: raw	157	0.58	(0.34-0.99)*

J Allergy Clin Immunol. 2011 Oct;128(4):766-773.e4

Cow milk proteins

@Tika

Cow‘s milk proteins

	apo-ALA	apo-BLG	apo-Serum albumin	apo-Lactoferrin	Casein micelle
monomers					
	α-lactalbumin	β-lactoglobulin	albumin	4OQO	
hexamer / dimer					
	1F6R	2AKQ	6QS9	Whey Proteins	Caseins
	1-1.5 g/L	3-4.5 g/L	0.1-0.4 g/L	0.5 mg/L	Approx. 30g/L
	Heat-labile				Heat-resistant

Nanoclusters of α–s1-casein, α–s2-casein, β-casein around calcium phosphate

hairy layer of κ-casein

@Tika

World Allergy Organ J. 2022 Sep 15;15(9):100668.

Cow milk proteins serve as micronutrient carrier

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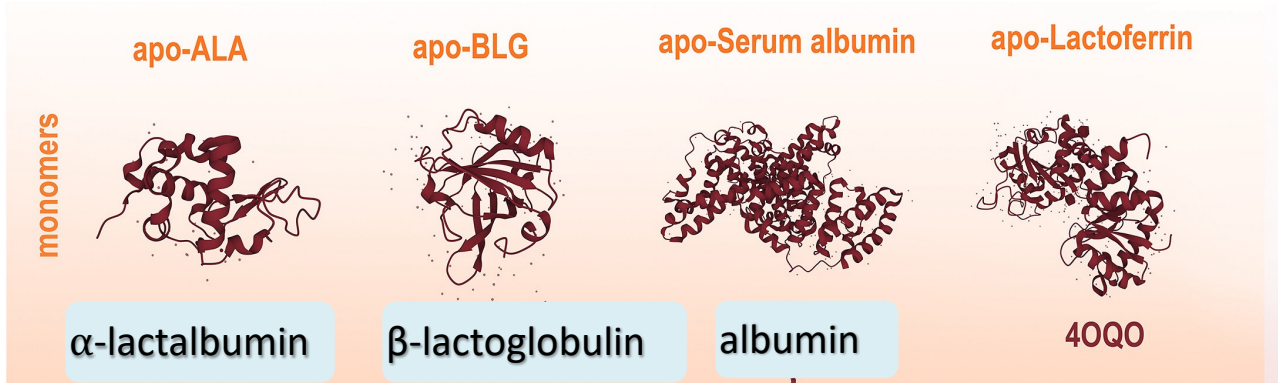

World Allergy Organ J. 2022 Sep 15;15(9):100668

@Tika

Heat-labile	Calcium Zinc, magnesium vitamins	Iron, selenium Lipids Flavonoids Amino acids polyphenols vitamins	Zinc Lipids Flavonoids Amino acids Proteins Hormones vitamins	Iron Lipids flavonoids	Phosphorus Calcium Aa with glutamine and proline Interaction with whey proteins

.

Biomed Res Int. 2018; 2018: 7523165.
Biomolecules . 2020 Aug 20;10(9):1210

Dietary lymphatic uptake of milk proteins

21167@pixabay

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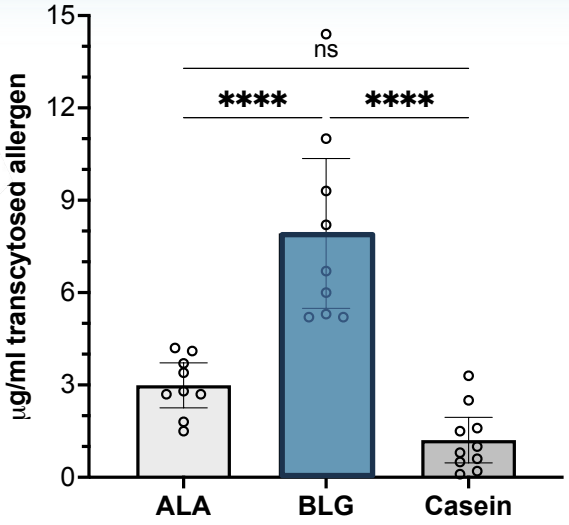
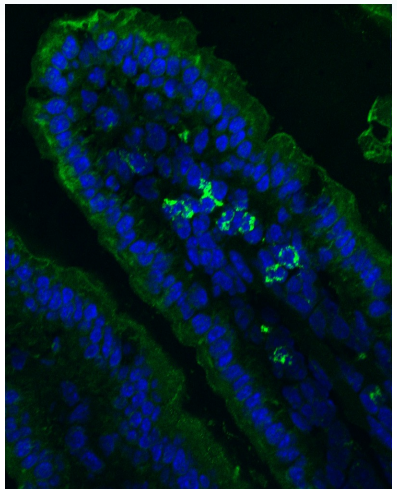
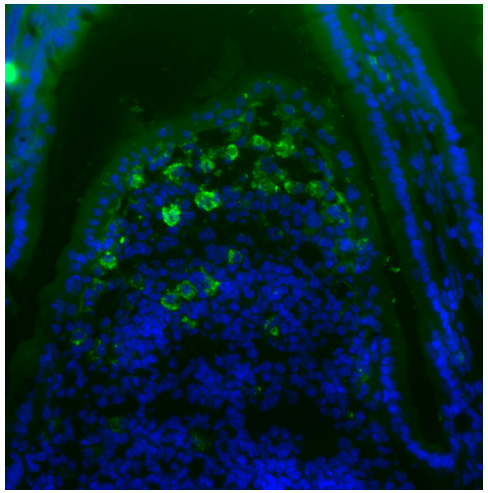
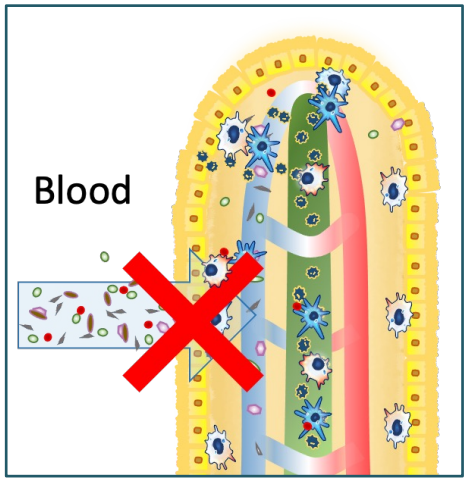






Allergy 2008 Jul;63(7):882-90.8



- cow whey proteins in the human milk of women

Int Arch Allergy Appl Immunol. 1984;75(1):8-15
J Nutr Sci Vitaminol (Tokyo). 1997;43(6):673-678

- post-prandial in the intestinal lymph

Proteomics. 2013;13(17):2649-2656.
Shock. 2014;42(6):485-498.

Impact of whey proteins with iron and vitamins

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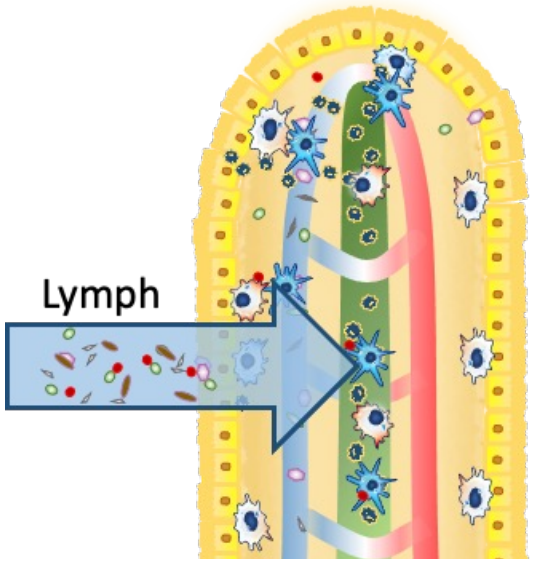


- iron fortified milk/whey proteins can significantly improve the iron status in children

JAMA Pediatr. 2021;175(8):790-796, Biometals. 2020;33(2-3):159-168, Am J Clin Nutr. 2018;107(2):278-286; Front Immunol. 2018;9:2123, Eur J Clin Nutr . 2008 Jan;62(1):39-50, Pediatrics. 2004;114(6):e699-706 Rev Med Chil. 1990;118(12):1330-1337

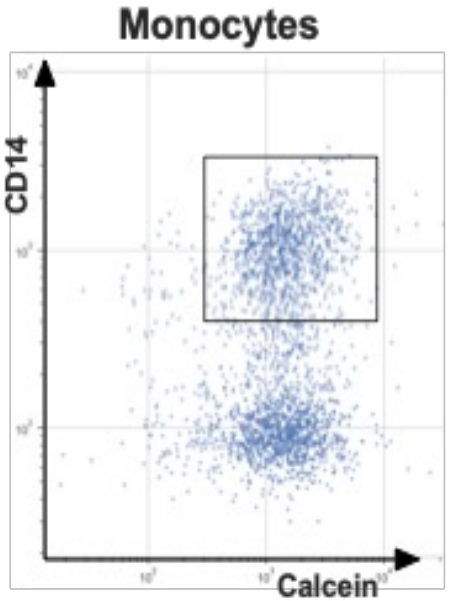
- 1 month whey-based oral supplement reduced IgE-levels and improved lung function in asthmatic children

Int J Food Sci Nutr 2006; 57(3-4): 204-11.

- RCT-trial: Micronutrient-fortified milk-beverages for 6 months reduced allergic manifestation by 36%

J Nutr J 2016; 15: 19.

Allergy-prevention with holo-BLG



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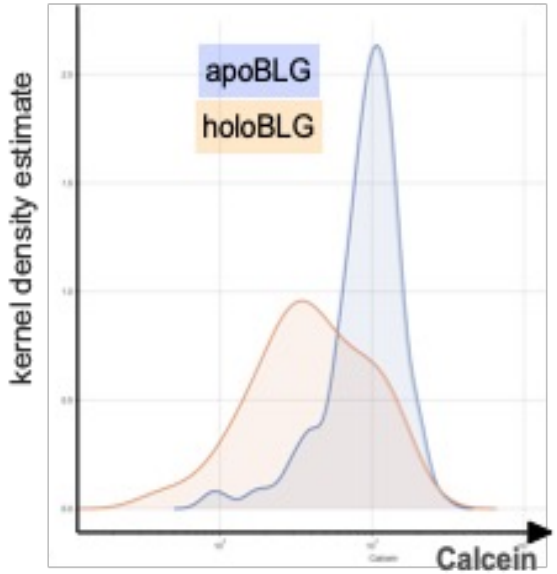

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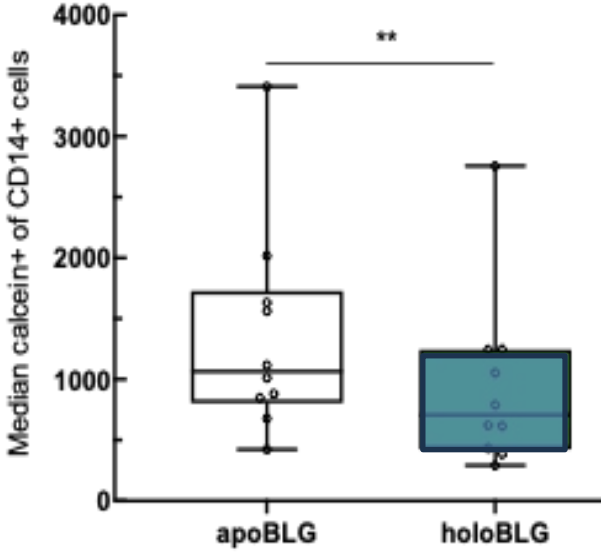
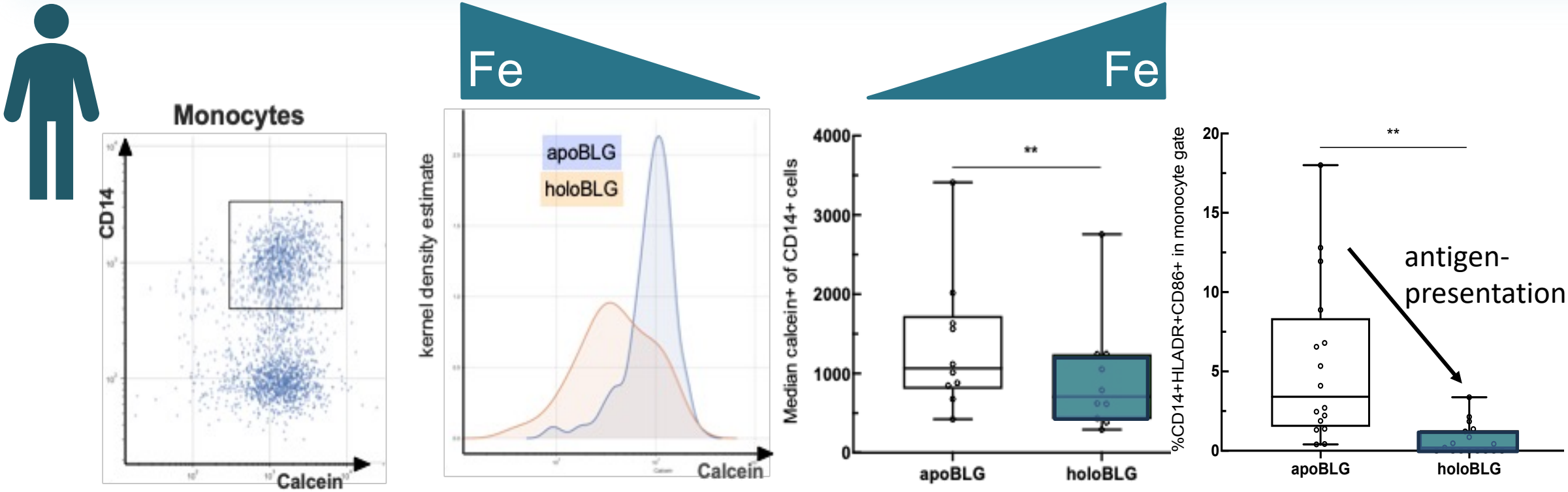


Holo-BLG supplies iron to immune cells

JACI 2021;147(1):321-334.e4

In vitro

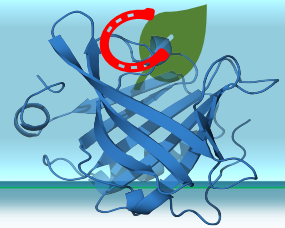
Allergy-prevention with holo-BLG



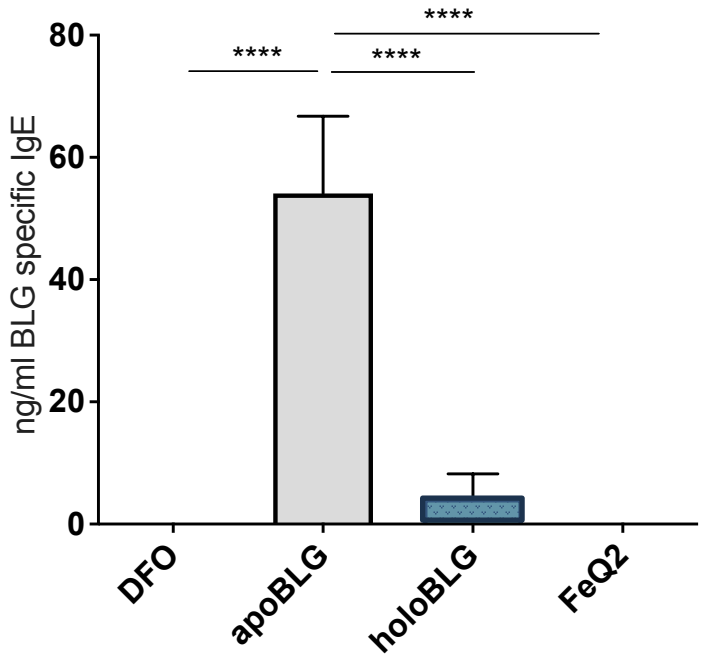
Supply of iron suppress immune cell activation

JACI 2021;147(1):321-334.e4

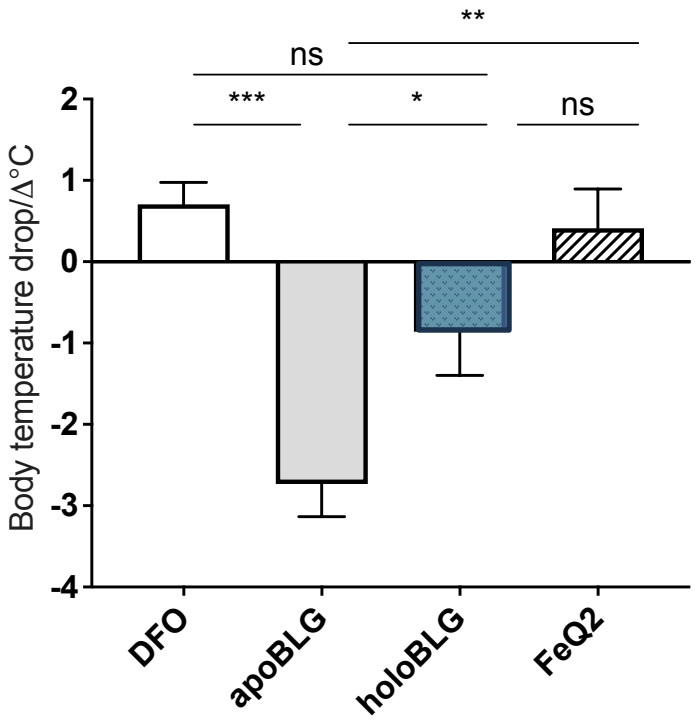
Allergy-prevention with holo-BLG



IgE



Body temperature



J. Rosenberg© flickrk

Holo-BLG prevents allergic sensitization

Front Immunol. 2021 Mar 5;12:611474.
Clin Exp Allergy. 2022 Mar;52(3):426-441.

JACI 2021;147(1):321-334.e4
NutritionNews 2020

Treating functional iron-deficiency

©Shutterstock_MykolaSamoilenko

to ameliorate atopic diseases

HoloBLG lozenge: Compensating micronutritional deficiencies in immune cells

HoloBLG Lozenge

- whey proteins: BLG
- catechines
- iron
- zinc
- vitamin A

} complex

Food for special medical purposes
(supplemental balanced diet)

„Immunonutrition“

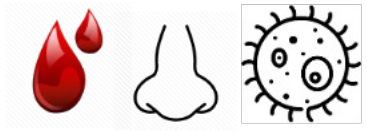
Study design

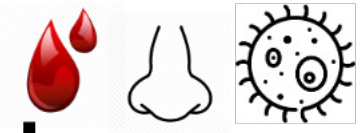
DBPC Study

allergic, Placebo lozenge n=26

allergic females; n=51

allergic, holoBLG lozenge n=25





Period 1
Screening
3 months

V1

V2

Period 2
supplementation

V3

2 months

Supplementation for 6 months

Nasal
Provocation

Nasal
Provocation

End of trial

V1 … Visit 1
V2 … Visit 2
V3 … Visit 3

Randomization

03/19

09/19

11/19

03/20

09/20

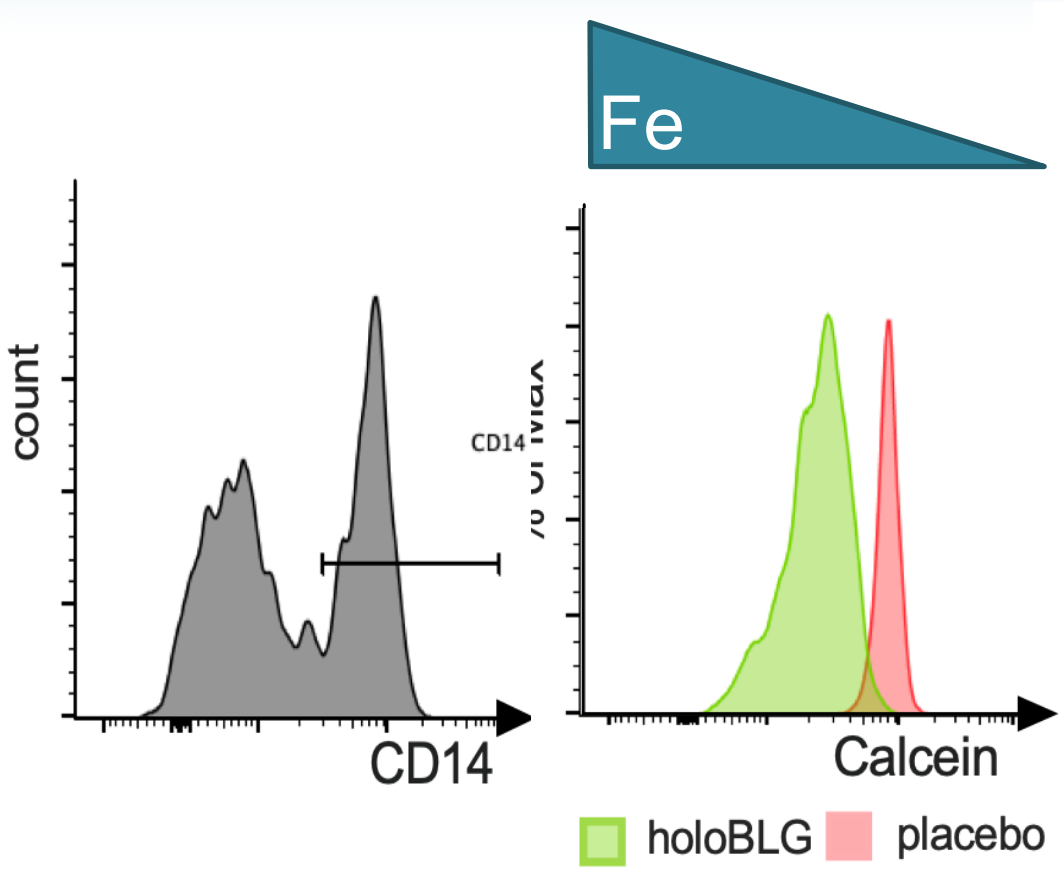
11/20

1st Lockdown

2nd Lockdown

COVID-19

HoloBLG increased labile iron in monocytes



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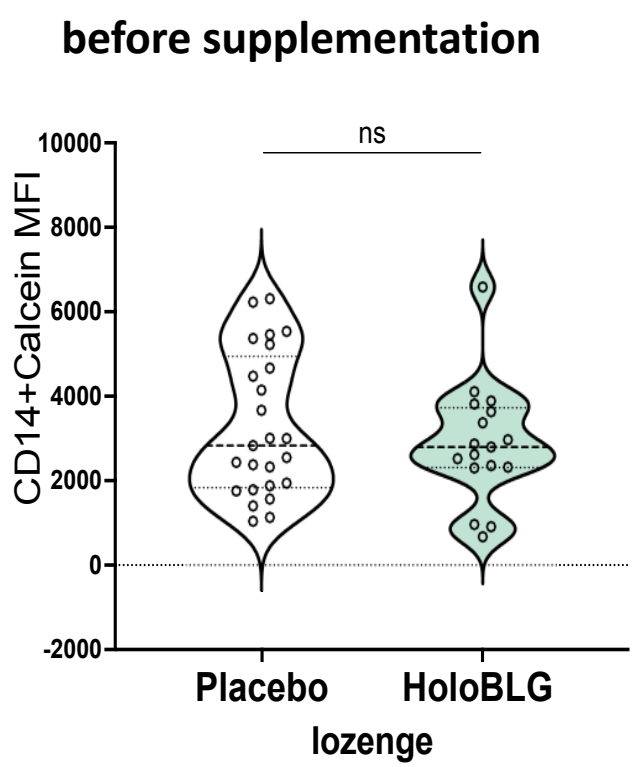
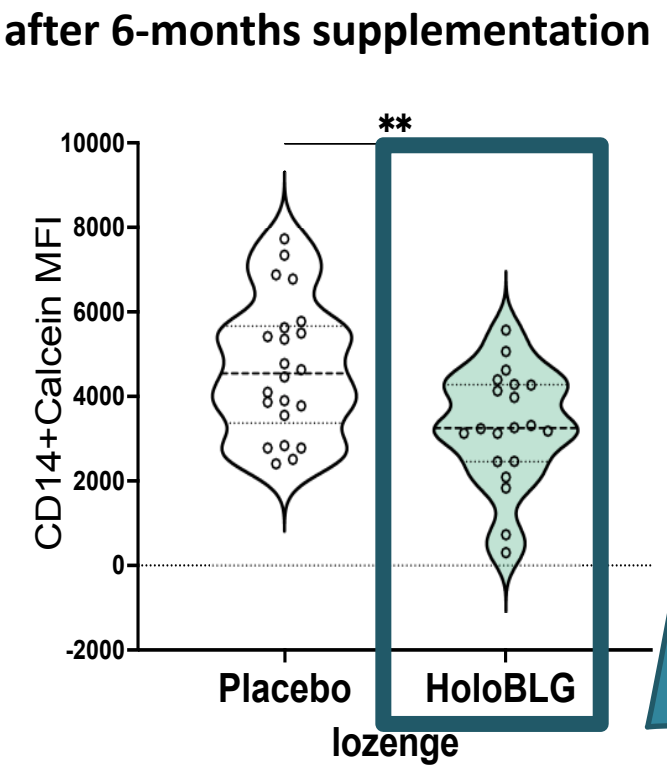




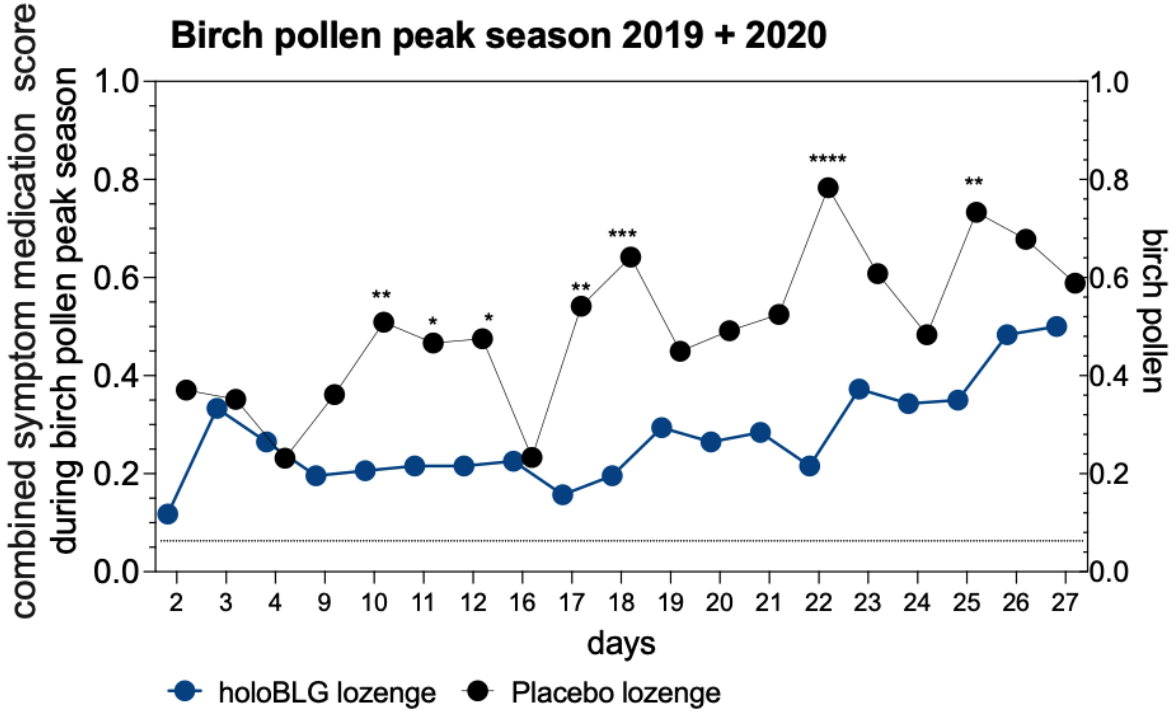
Iron

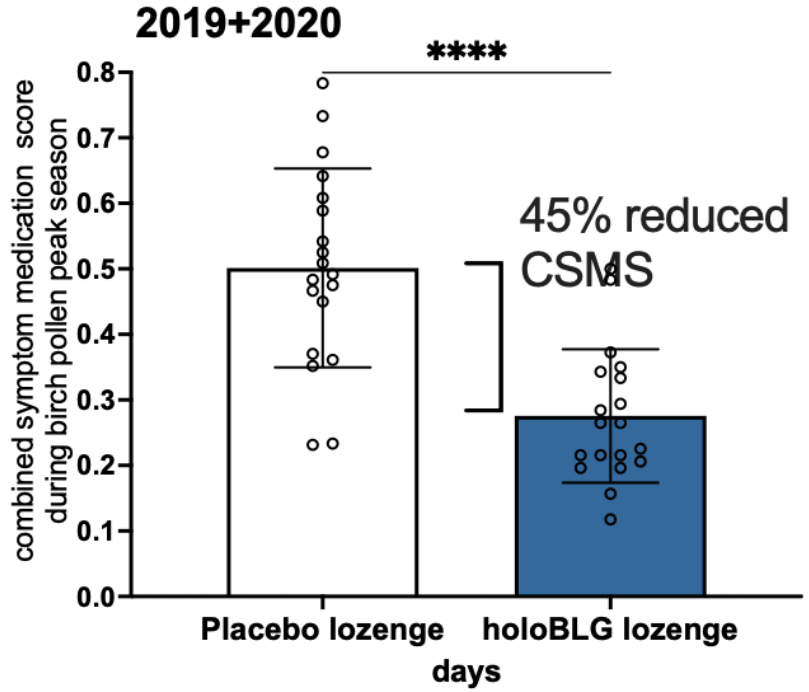
Bartosik et al., J Allergy Clin Immunol Pract. 2022 Mar 6:S2213-2198(22)00229-X

holoBLG: Reduced symptom burden in the birch season

pollenwarndienst.at

filmfoto © iStock



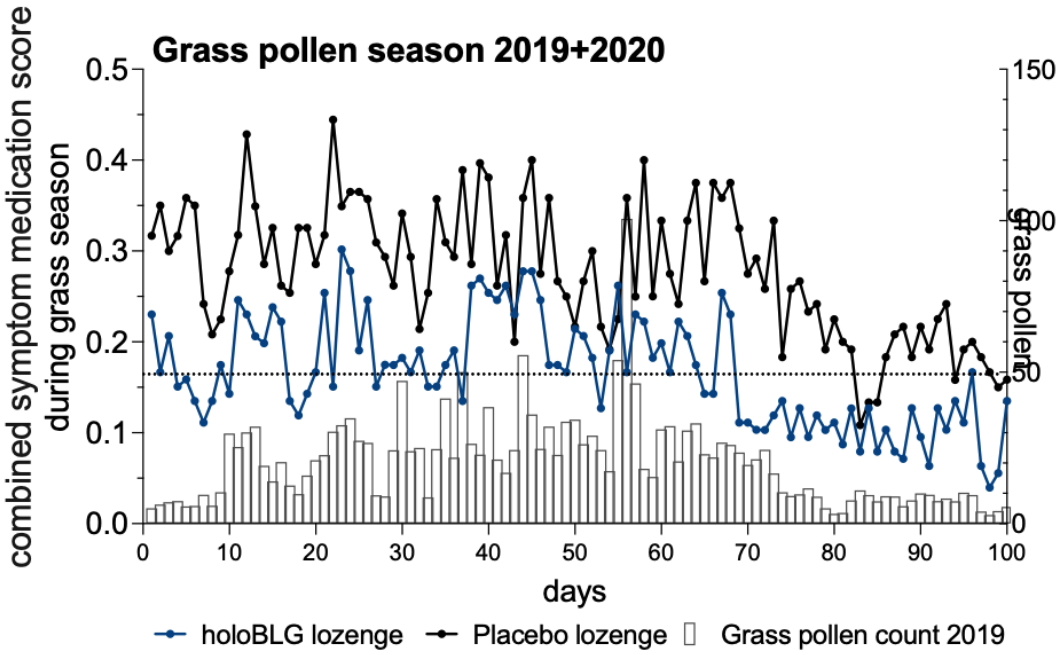


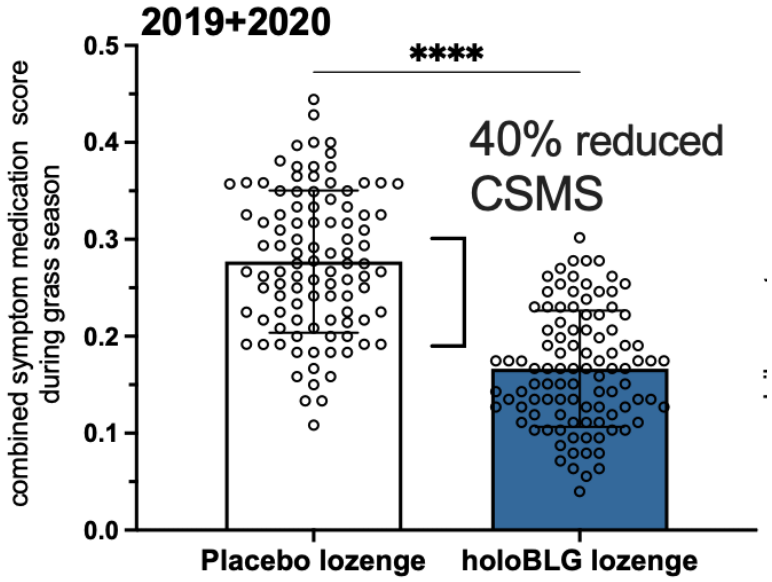
Bartosik et al., J Allergy Clin Immunol Pract. 2022 Mar 6:S2213-2198(22)00229-X

holoBLG: Reduced symptom burden in the grass pollen season

pollenwarndienst at

Am124_014 © evermotion





Bartosik et al., J Allergy Clin Immunol Pract. 2022 Mar 6:S2213-2198(22)00229-X

holoBLG: Reduced symptom burden

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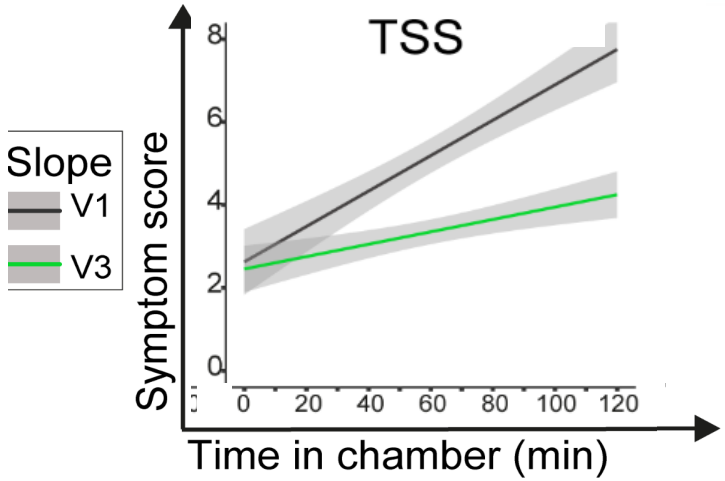
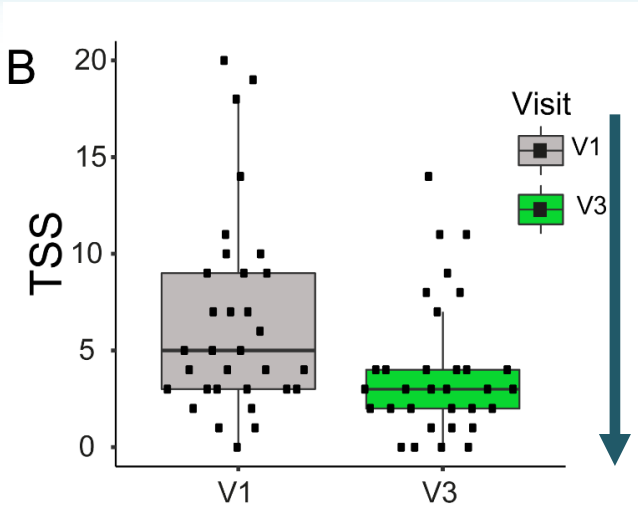




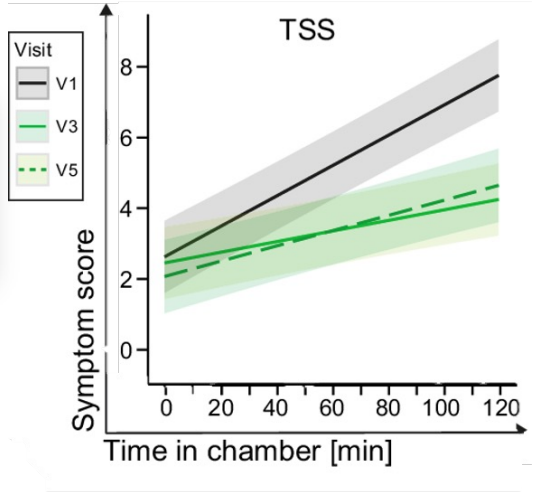
Study in 32 in house dust mite allergics

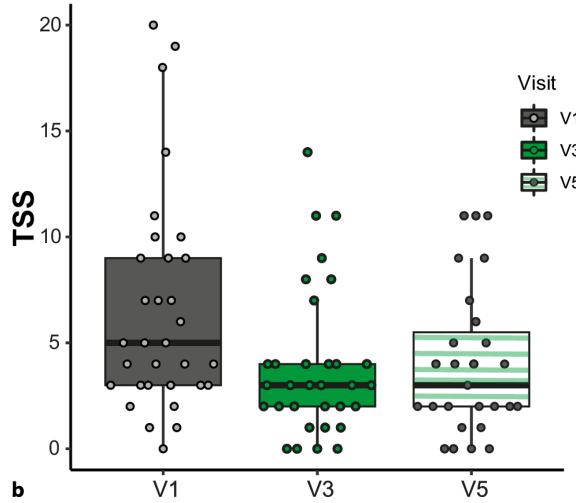
-40%

Bergmann, KC *et al. Allergo J Int 2021; 30: 141-149*

Lasting effect

7-8 months later





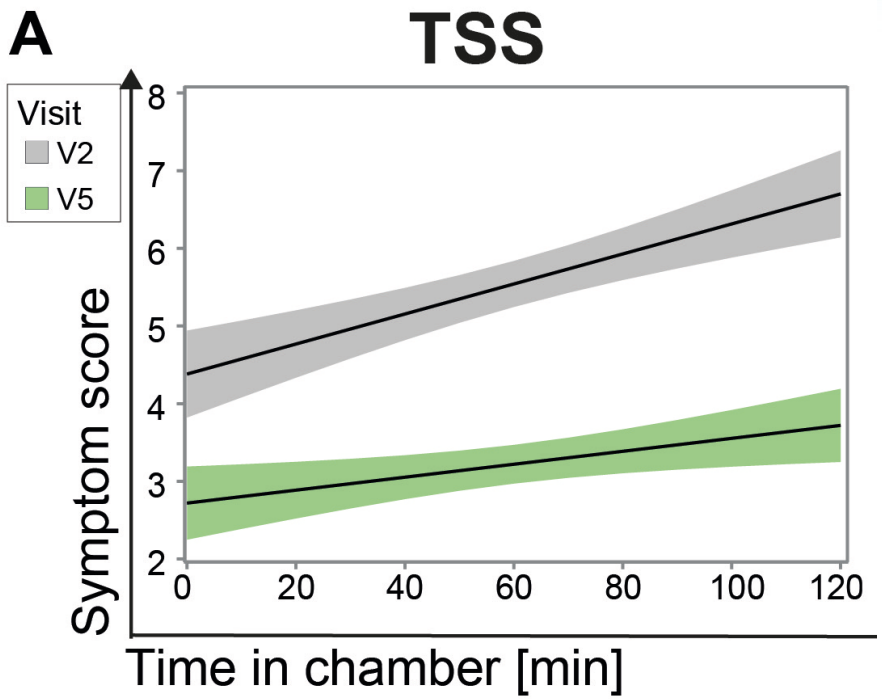
-40%

<u>Follow-up study</u> with 27 of the 32 house dust mite allergic subjects

Bergmann, KC et al. *Allergo J Int 2022; 31: 161-171*

holoBLG: Reduced symptom burden

ingmar1989 © flickr



-50%

in 35 cat allergic patients

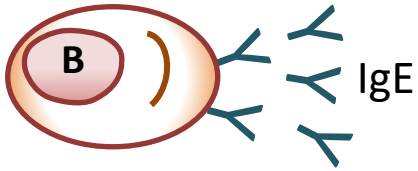
3-month intervention

median TSS reduction of 50%

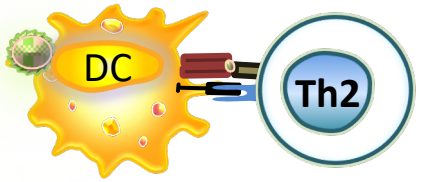
Clin Transl Allergy 2023 Jul;13(7):e12274

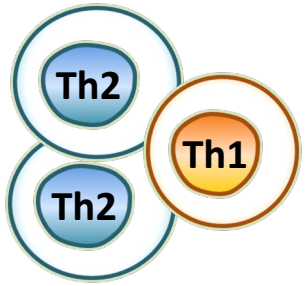
Conclusion

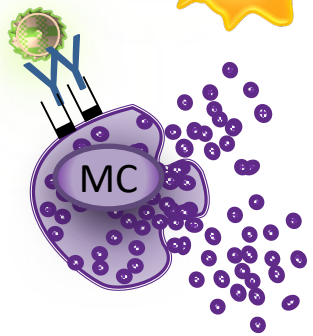
Inflammation

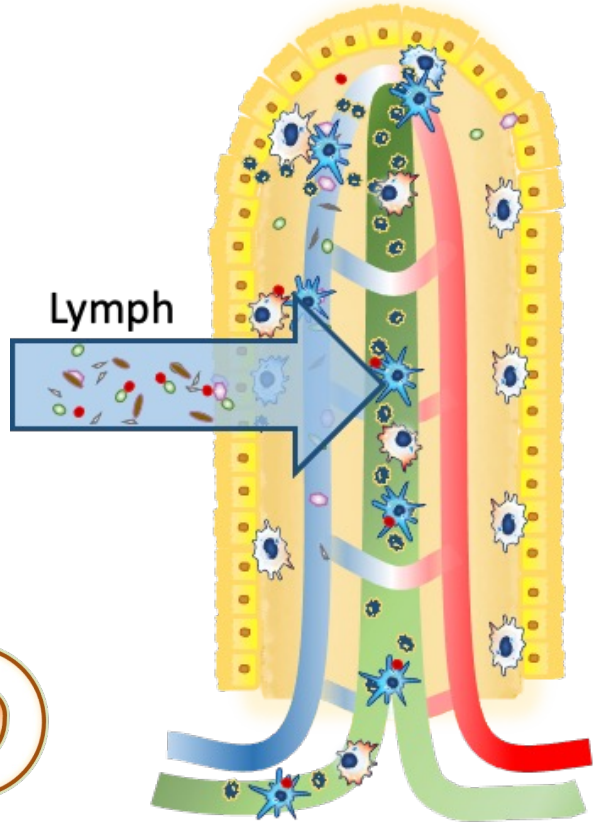


IL4 IL13

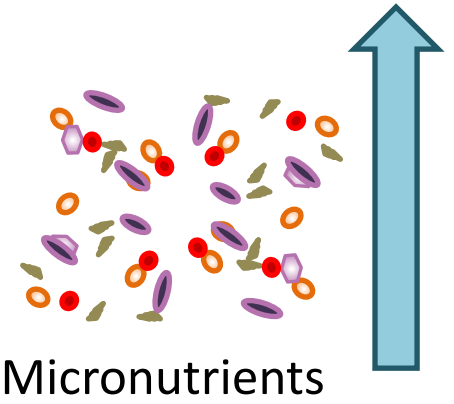








Health



Micronutrients

deficient

sufficient

vetmeduni

messerli Research Institute

MEDICAL UNIVERSITY OF VIENNA

pollenwarndienst.at

Bencard Allergie

biomedical Int. R&D

AMICI Austrian Microbiome Initiative

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