The Environmental Determinants of Diabetes in the Young - The TEDDY study with a focus on paediatric coeliac disease

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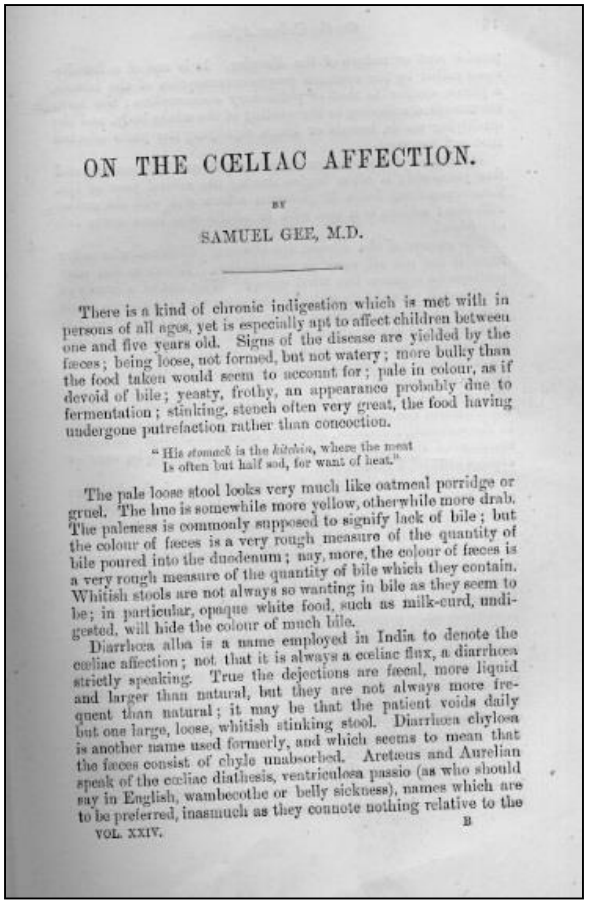
“If the patient can be cured at all, it must be by the means of diet.”

Gee, SJ (1888). "On the coeliac affection". St Bartholomew's Hospital Report. 24: 17–20.



ON THE CŒLIAC AFFECTION.

BY

SAMUEL GEE, M.D.

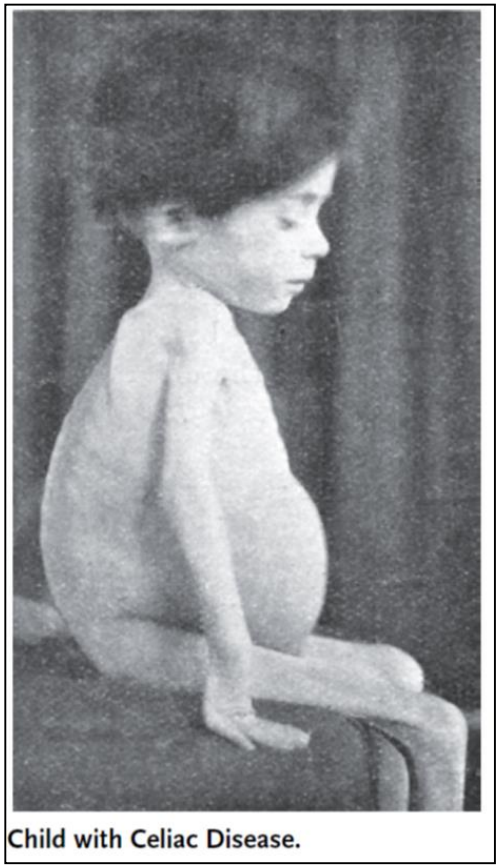
There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children between one and five years old. Signs of the disease are yielded by the fæces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for; pale in colour, as if devoid of bile; yeasty, frothy, an appearance probably due to fermentation; stinking, stench often very great, the food having undergone putrefaction rather than concoction.

“His *stomack* is the *kitchin*, where the meat
Is often but half sod, for want of heat.”

The pale loose stool looks very much like oatmeal porridge or gruel. The hue is somewhile more yellow, otherwhile more drab. The paleness is commonly supposed to signify lack of bile; but the colour of fæces is a very rough measure of the quantity of bile poured into the duodenum; nay, more, the colour of fæces is a very rough measure of the quantity of bile which they contain. Whitish stools are not always so wanting in bile as they seem to be; in particular, opaque white food, such as milk-curd, undigested, will hide the colour of much bile.

Diarrhœa alba is a name employed in India to denote the cœliac affection; not that it is always a cœliac flux, a diarrhœa strictly speaking. True the dejections are fæcal, more liquid and larger than natural, but they are not always more frequent than natural; it may be that the patient voids daily but one large, loose, whitish stinking stool. Diarrhœa chylosa is another name used formerly, and which seems to mean that the fæces consist of chyle unabsorbed. Aretæus and Aurelian speak of the cœliac diathesis, ventriculosa passio (as who should say in English, wambecothe or belly sickness), names which are to be preferred, inasmuch as they connote nothing relative to the

From a rare to a common disease



Child with Celiac Disease.

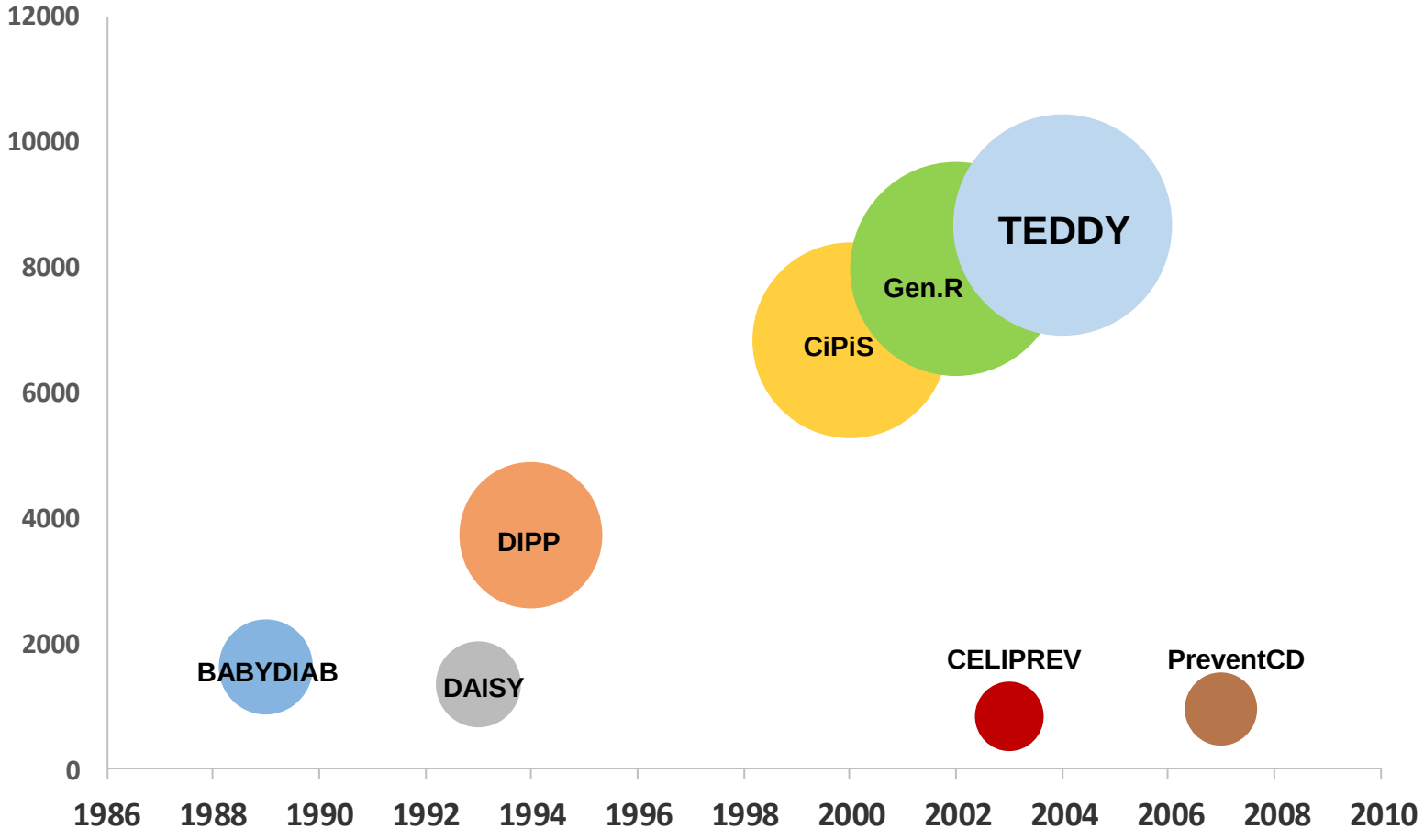
Losowsky MS. A history of coeliac disease. Dig Dis. 2008;26(2):112-20.

Most cases are detected by screening

Ivarsson et al. Prevalence of childhood celiac disease and changes in infant feeding. Pediatrics 2013 Mar;131(3):e687-94.

Prospective birth cohorts

Prospective screenings for coeliac disease



TEDDY

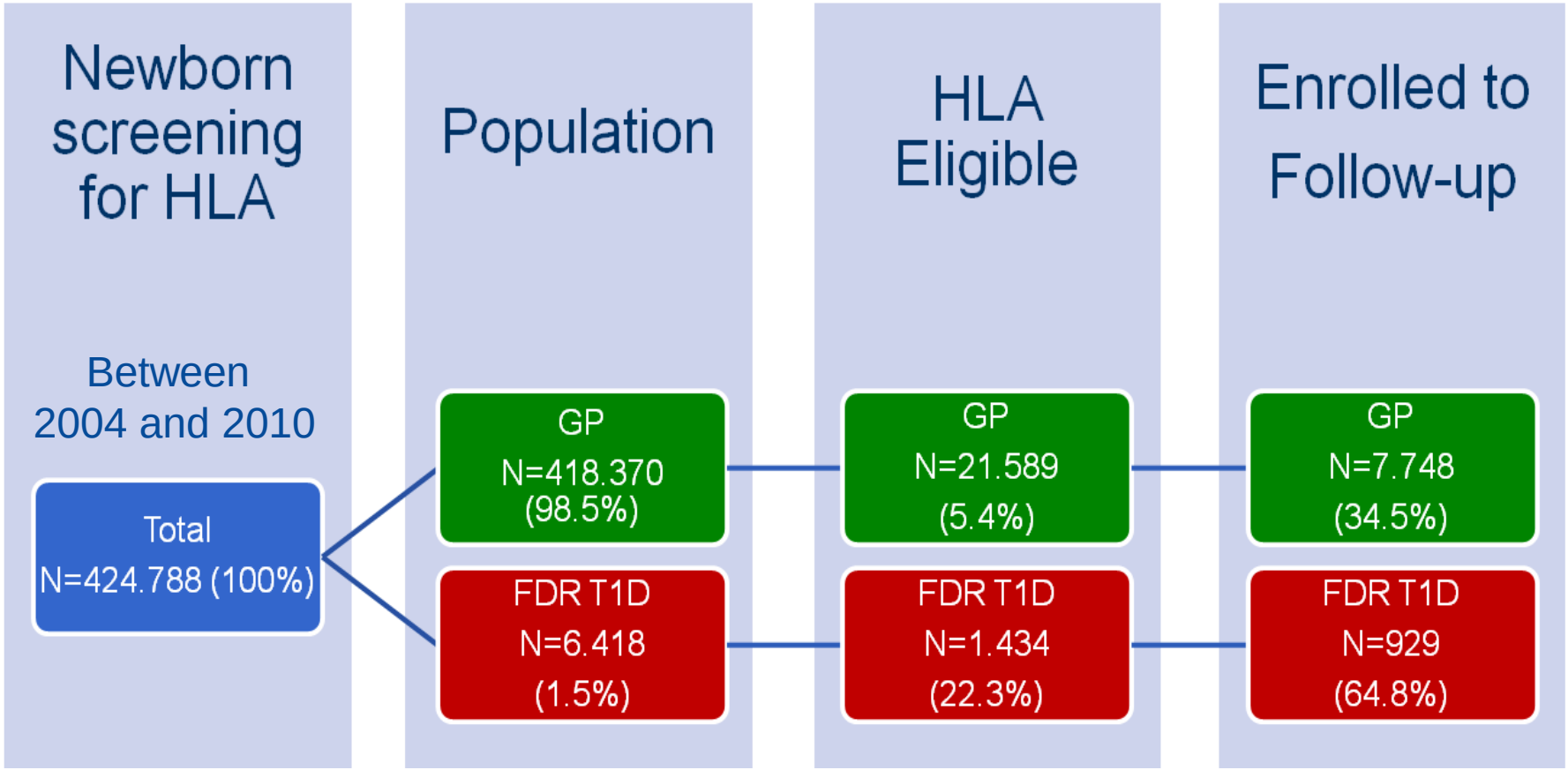
The Environmental Determinants of Diabetes in the Young (TEDDY)

Overall goal: To identify environmental and genetic factors associated with **type 1 diabetes** and **coeliac disease**.

Design: Observational multicenter study with a 15-year follow-up at 6 clinical centers in **Finland**, **Germany**, **Sweden** and **Colorado, Georgia, Washington states** in the US.

Population: HLA-risk children from the general population prospectively followed from birth to 15 years of age.

Enrollment of 8667 newborns at HLA risk



HLA-risk genotypes:DR3-DQ2/DR3-DQ2; DR3-DQ2/DR4-DQ8; DQDR4-DQ8/DR4-DQ8; DR4-DQ8/X; DR4-DQ8/DR8,DR4/DR,DR4/DR13, DR4/DR9 (only in FDR with T1D)

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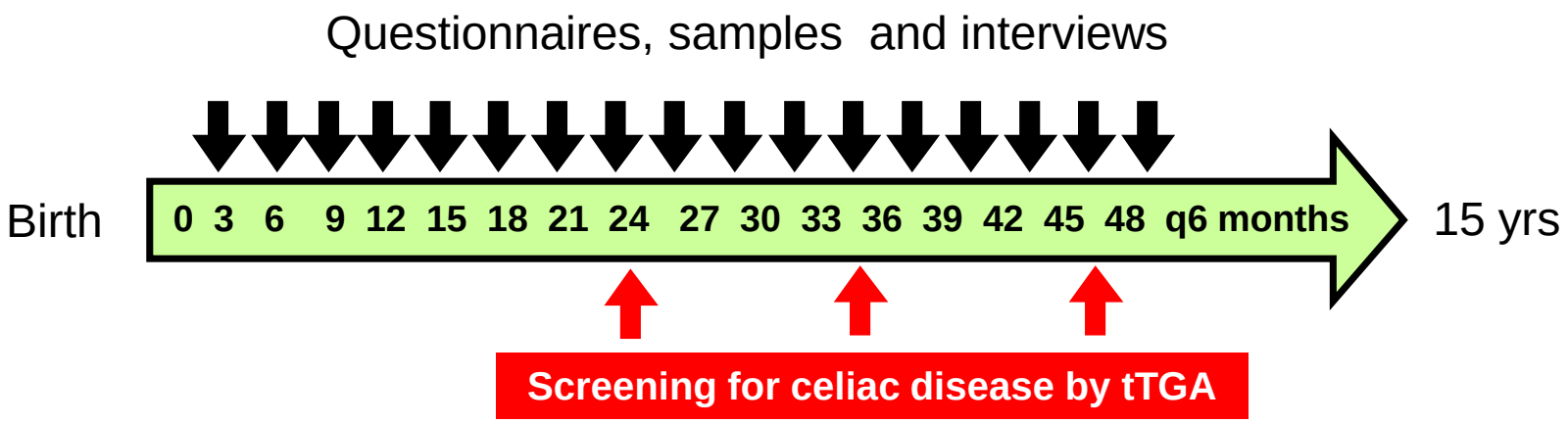
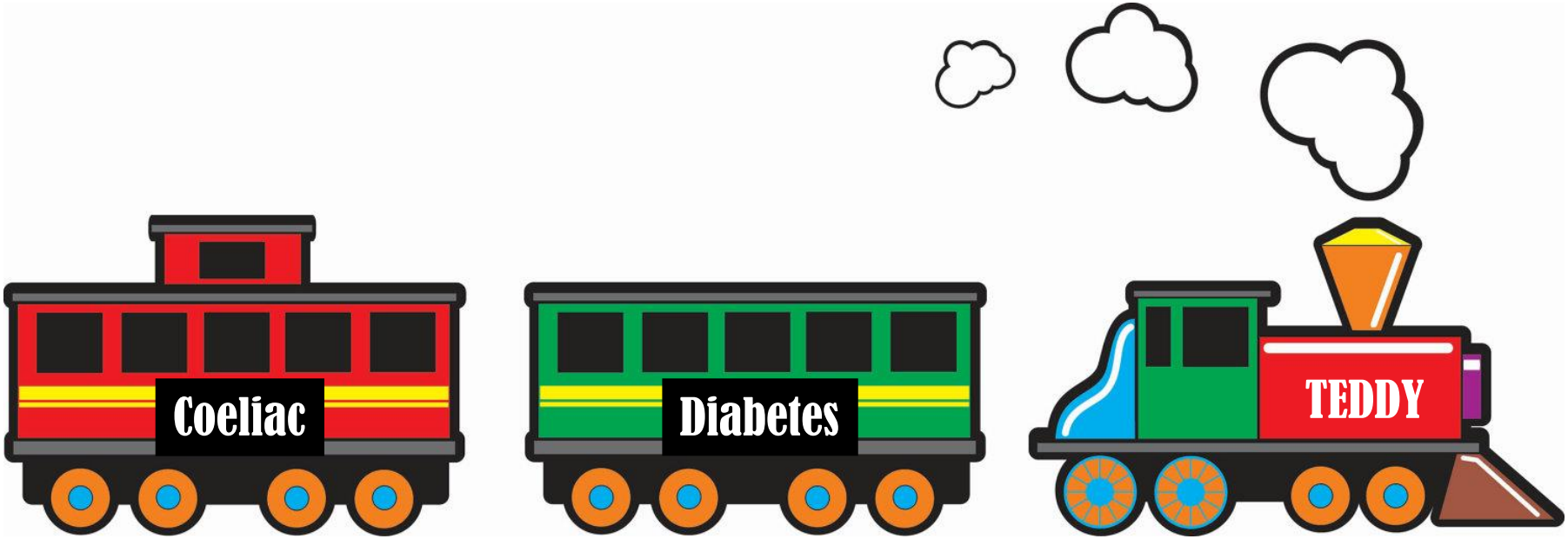
TEDDY protocol



Clinic visits every 3 months (including ab+ children older than 4):

- **Blood for:** GADA, IAA, IA-2A, ZnT8A; tTGA, TPOA, ThgA, DNA, RNA, infectious agents, HbA1c, PBMC, erythrocytes, storage plasma/serum.
- **Stool, urine, nasal swabs, tap water, toenail clippings, teeth, saliva**.
- **Interviews:** maternal pregnancy diet, infection and smoking; child's 24 hr recall, 3 day FFQ; negative life events, parental anxiety, depression, records of infections, medications, immunizations; family history, child experiences; re-enrollment of subjects lost; Physical activity assessment; ht, wt, body composition measurements;DNA from FDRs

The TEDDY Study



2004
Start

2017
Half way there

2025
End station

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Visits & samples as of April 30, 2017

Completed Visits	N=160,469
Completed Questionnaires	N=633,573
Blood Samples	N=3,517,179
Nasal Swabs	N=97,605
Stool Samples	N=615,494
Urine Samples	N=87,878
tTGA measurements	N=52,431
Coeliac disease	N=454

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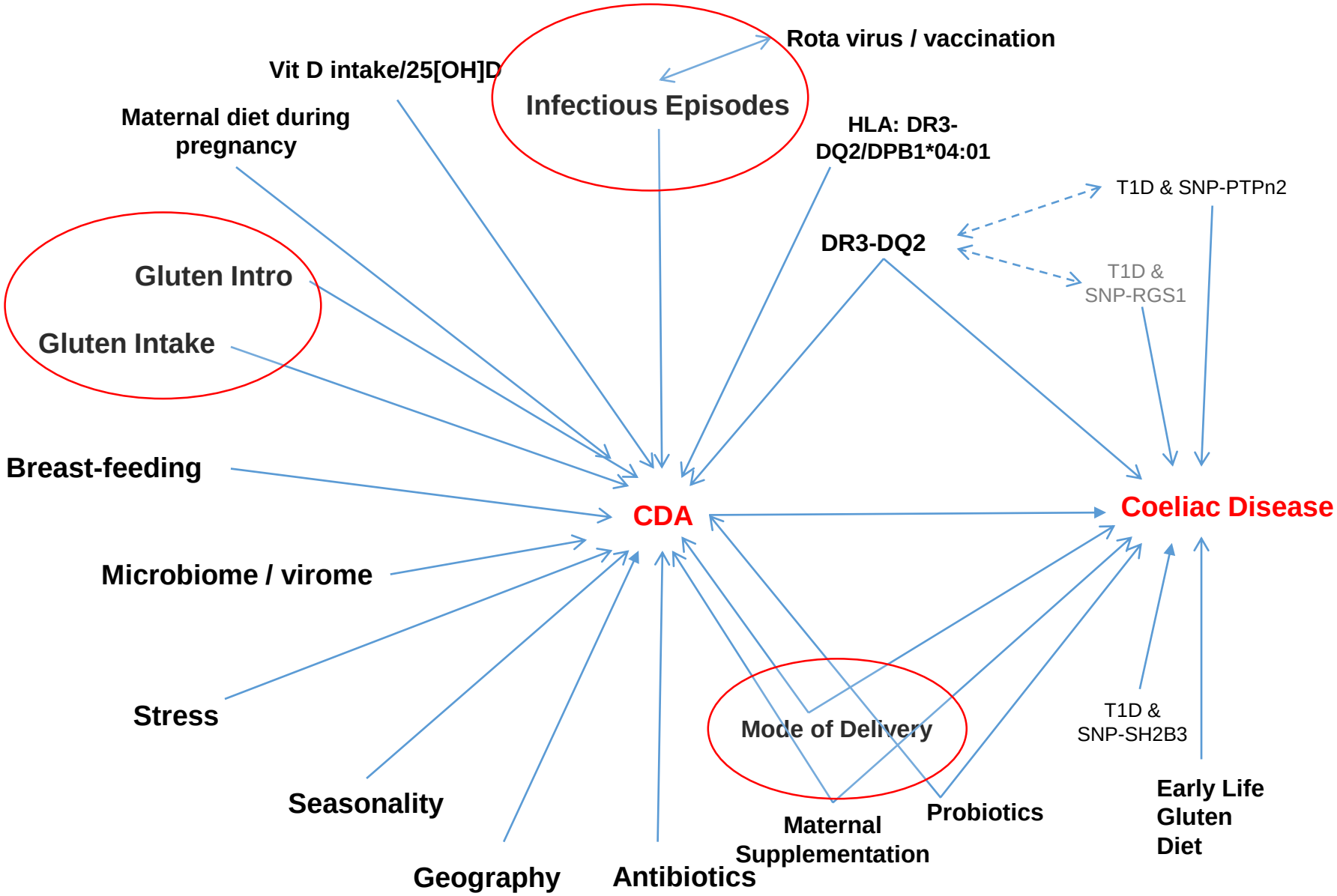

CDA; coeliac disease autoimmunity, i.e. persistent tTGA.

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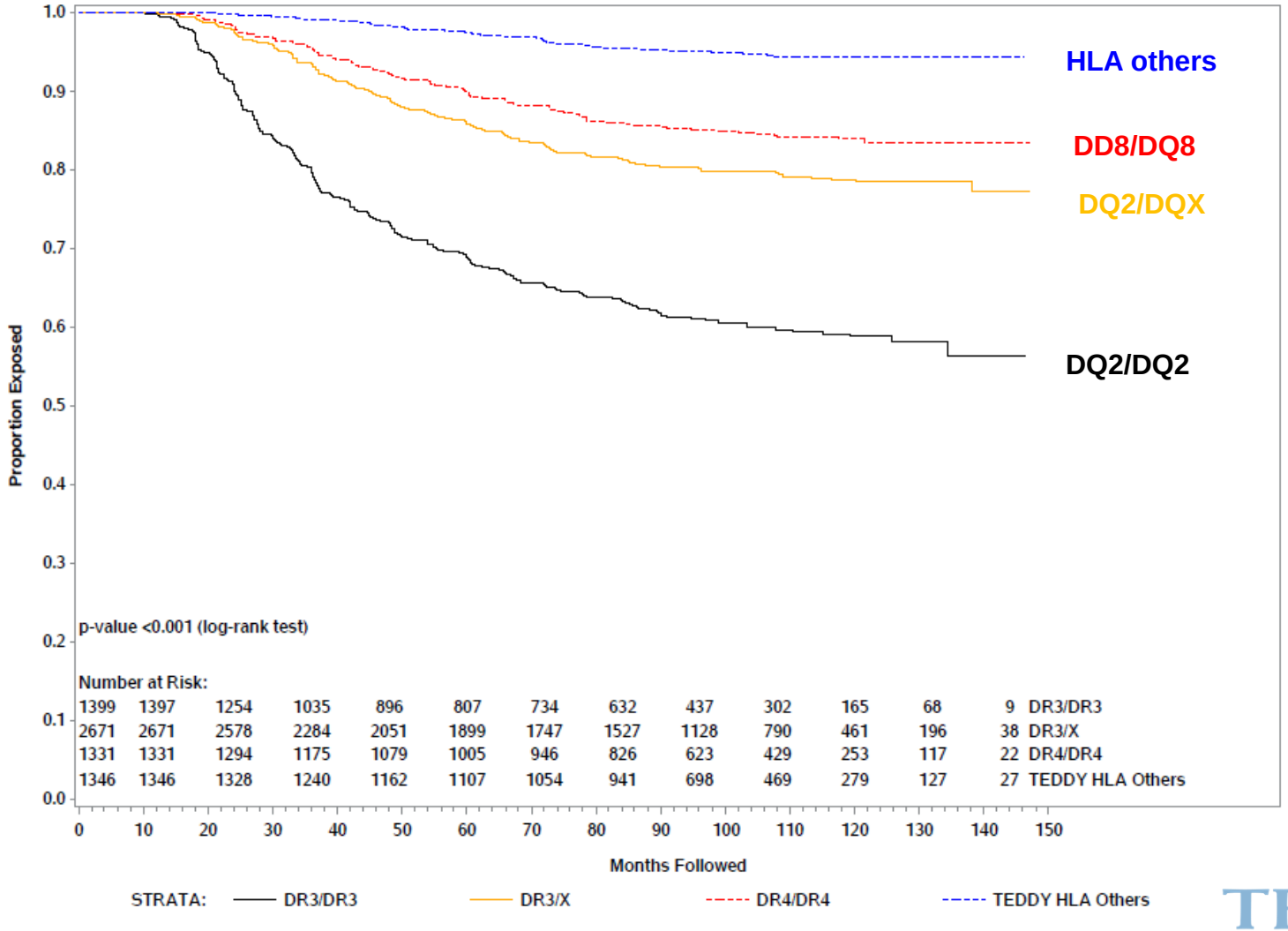
TEDDY midterm results

Time to coeliac disease autoimmunity by HLA



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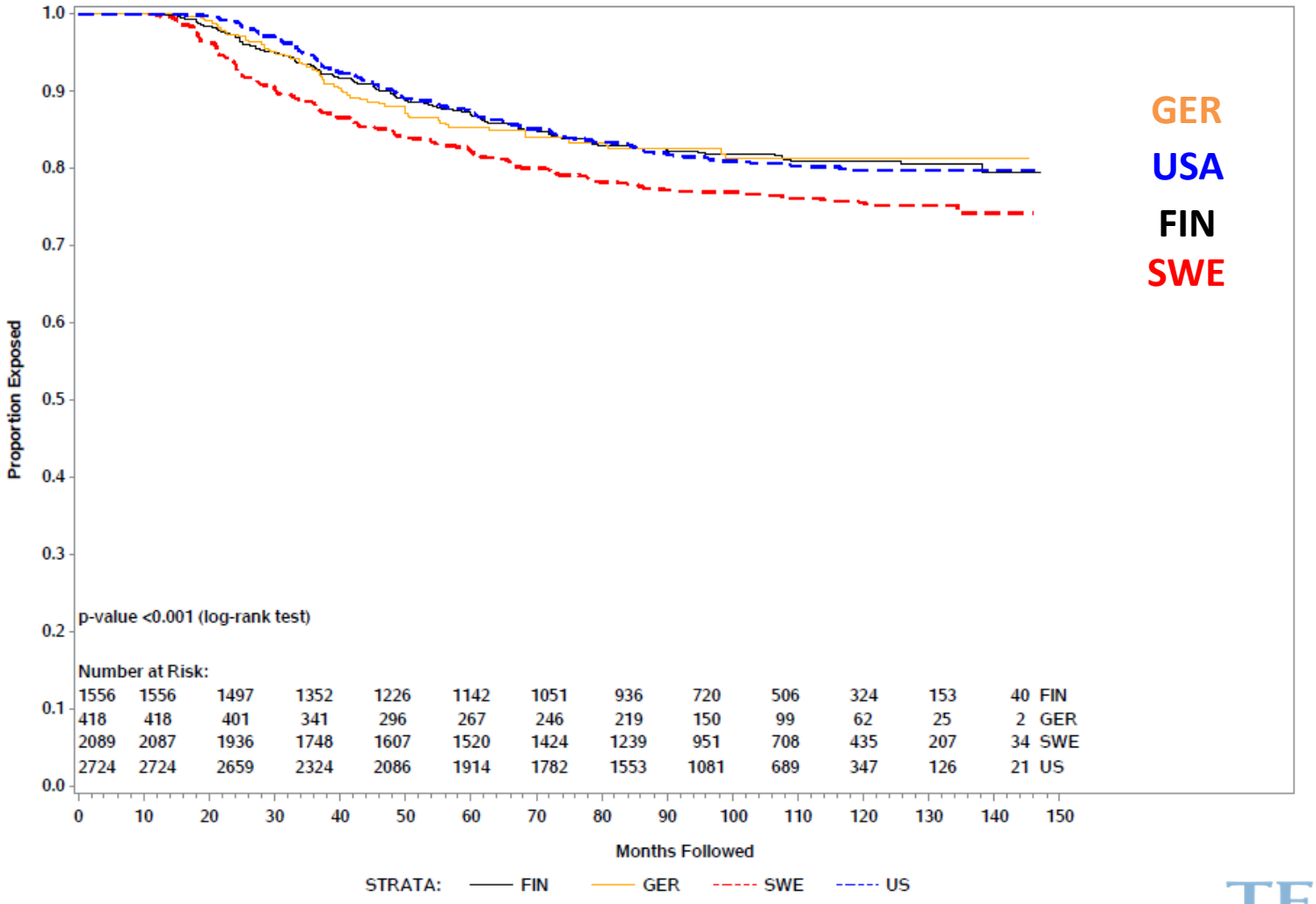
Time to coeliac disease autoimmunity by Country



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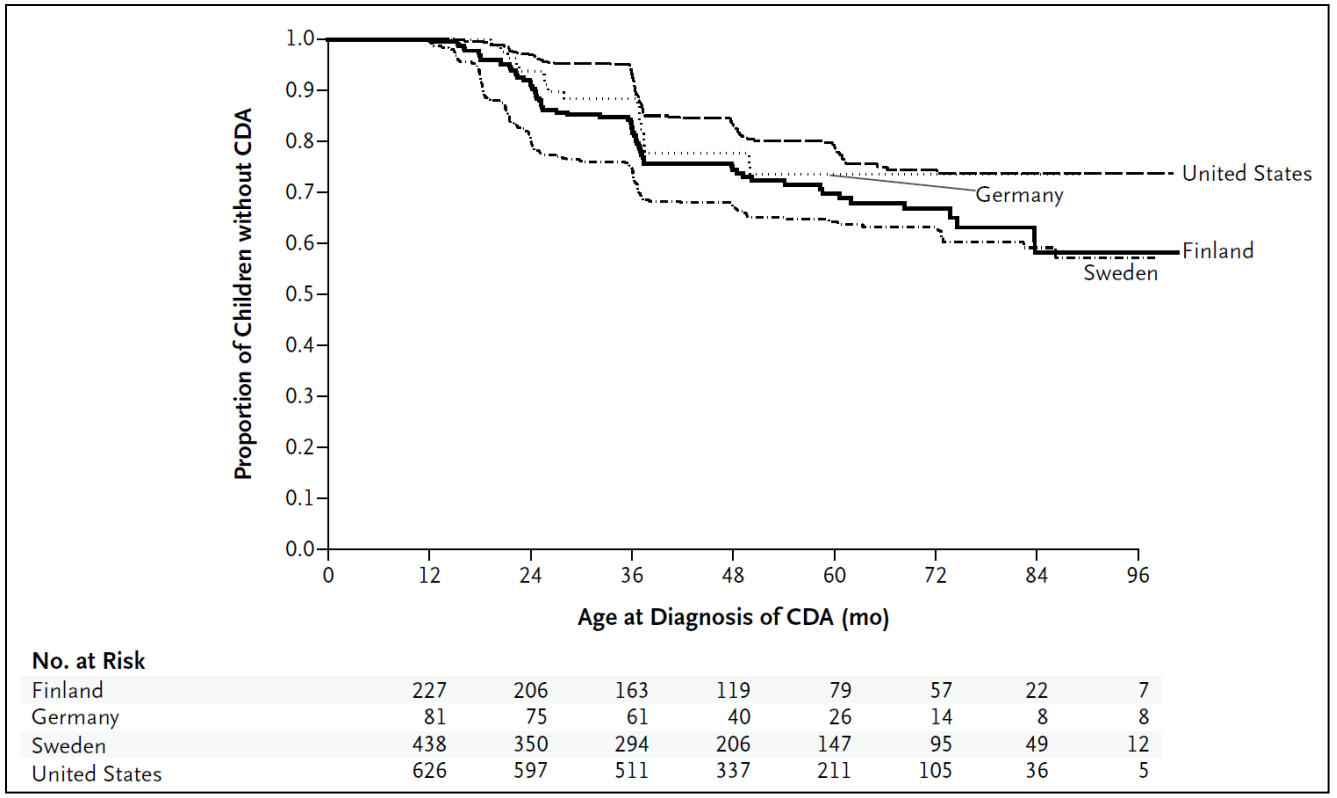
Risk of paediatric coeliac disease according to HLA haplotype and Country



No. at Risk								
Finland	227	206	163	119	79	57	22	7
Germany	81	75	61	40	26	14	8	8
Sweden	438	350	294	206	147	95	49	12
United States	626	597	511	337	211	105	36	5

Residence in Sweden independently associated with a 2-fold increased risk of celiac disease autoimmunity in TEDDY

Liu et al. N Engl J Med. 2014 Jul 3;371(1):42-9.

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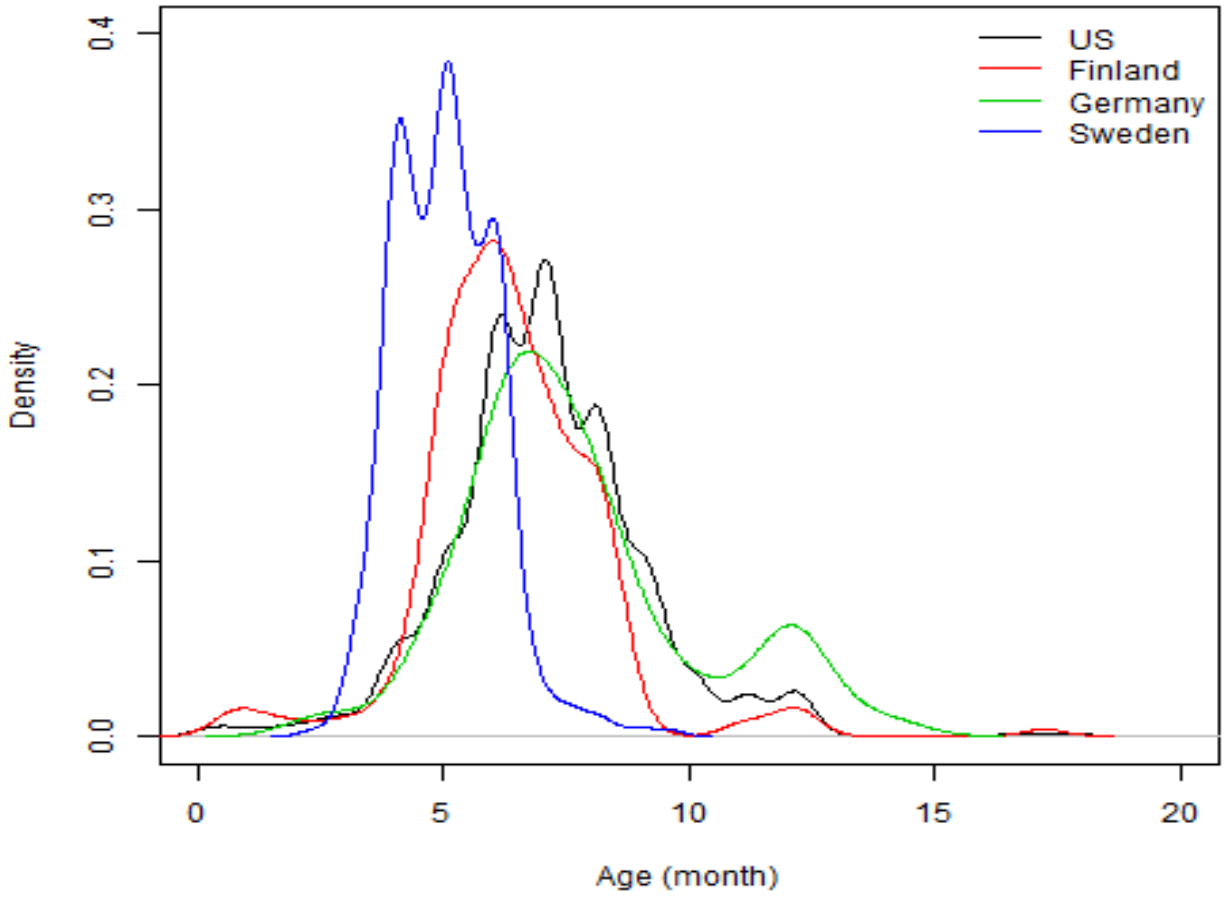
Gluten

Time to first introduction of gluten by Country



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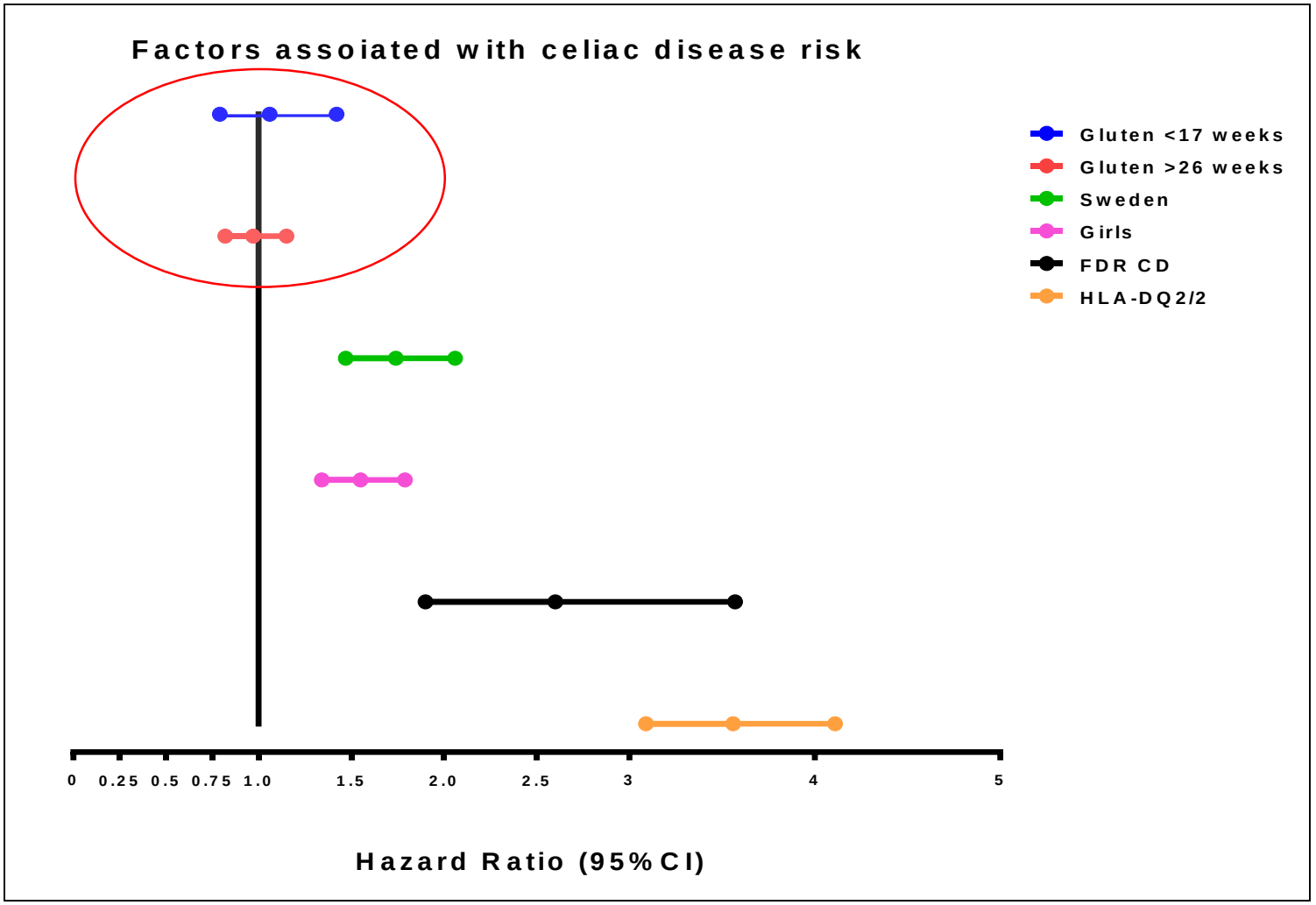
Age at gluten introduction and coeliac disease



Aronsson et al Pediatrics. 2015 Feb;135(2):239-45.

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AP&T Alimentary Pharmacology and Therapeutics

Systematic review with meta-analysis: early infant feeding and coeliac disease – update 2015

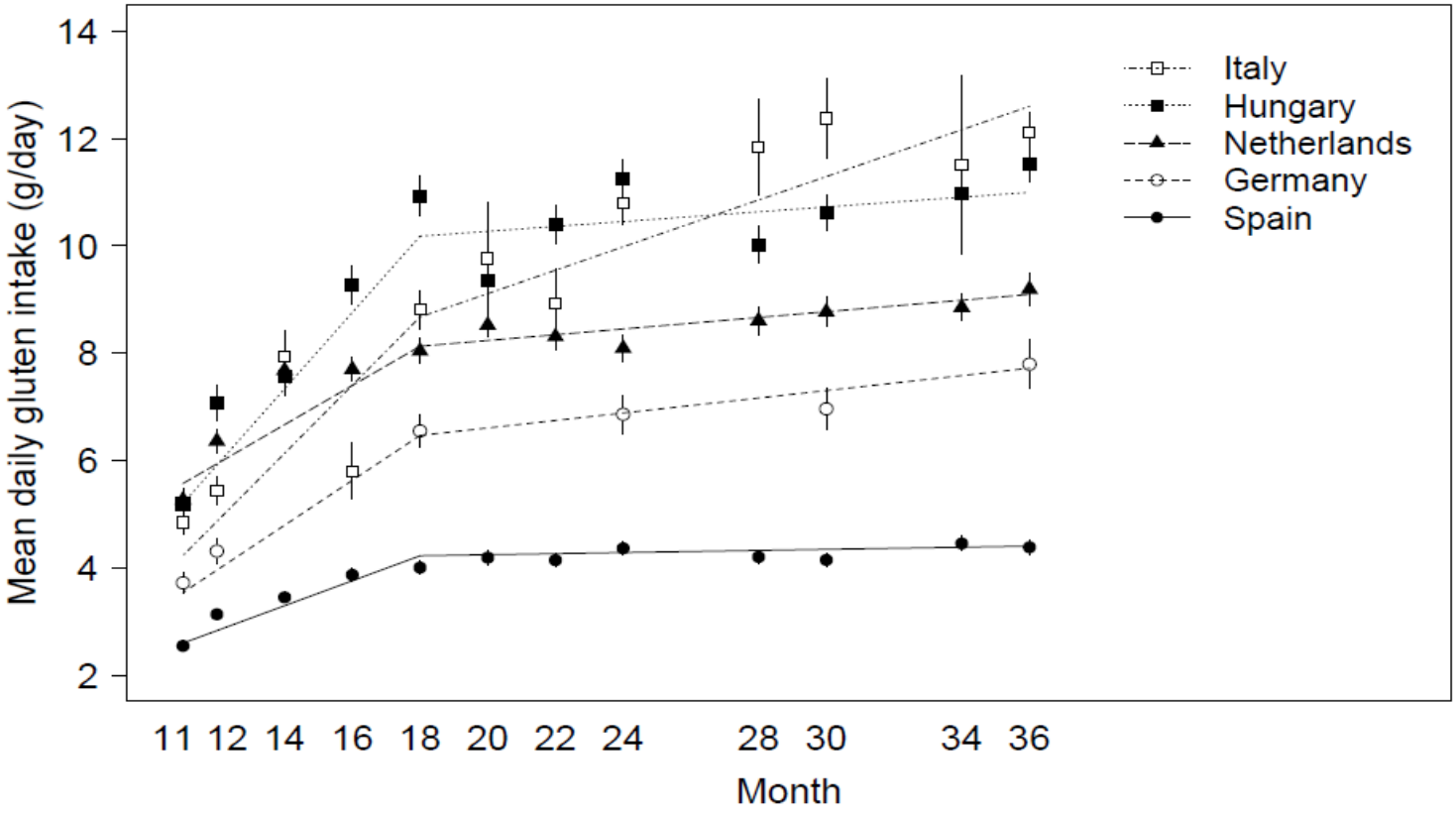
H. Szajewska*, R. Shamir†, A. Chmielewska*, M. Pieścik-Lech*, R. Auricchio‡, A. Ivarsson§, S. Kolacek¶, S. Koletzko**, I. Korponay-Szabo††, M. L. Mearin‡‡, C. Ribes-Koninckx§§ & R. Troncone‡ on behalf of the PREVENTCD Study Group[a]

Conclusion: Breastfeeding and time of gluten introduction have *no* effect on the risk of developing coeliac disease during childhood.

Szajewska et al. Aliment Pharmacol Ther. 2015; 41(11):1038-1054.

The role of gluten consumption at an early age in celiac disease development

PreventCD study

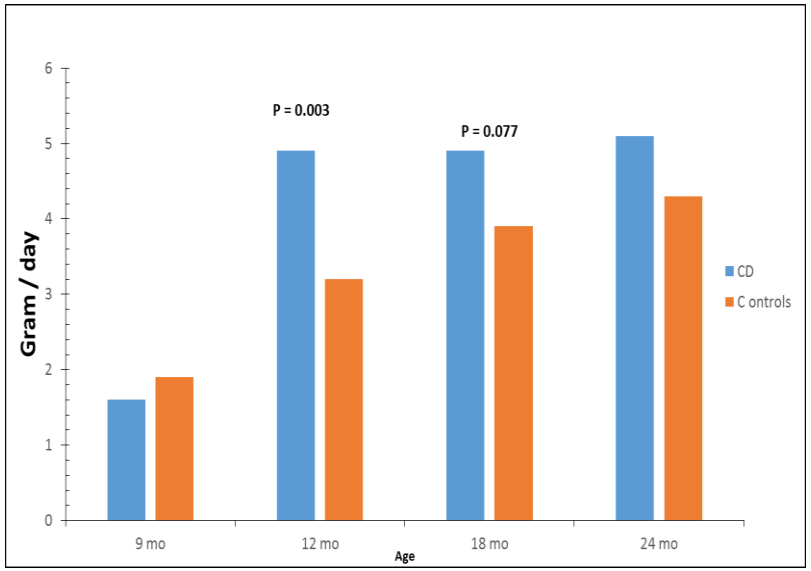


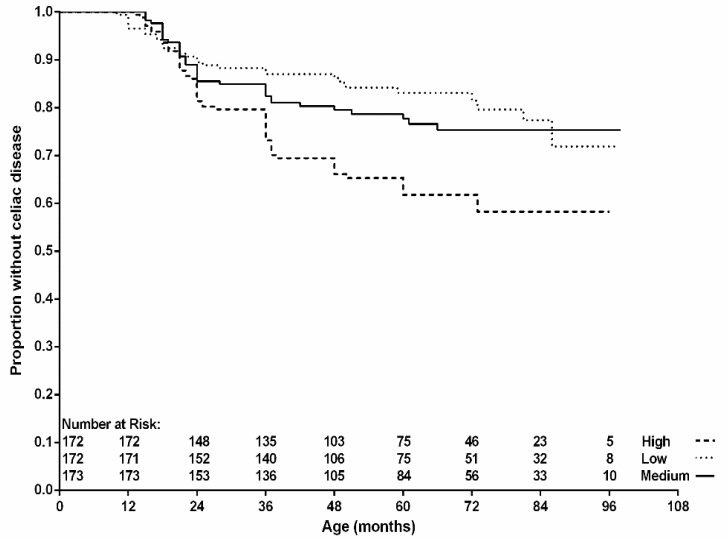
Conclusion: No association between high intake of gluten and increased risk of coeliac disease after 11 months of age**.**

Crespo-Escobar P et al. Am J Clin Nutr. 2017 Apr;105(4):890-896.

Effects of gluten intake on risk of coeliac disease: A case-control study on a Swedish birth cohort

Amount of gluten <2 years of age in 1-to-3 nested case-control study of 146 cases, resulting in 436 case-control pairs matched for sex, birth year, and HLA.





Conclusion: High intake of gluten amounts before 2 years of age increases the risk of celiac disease (at least in Swedish children).

Andrén Aronsson et al. Clin Gastroenterol Hepatol. 2016 Mar;14(3):403-409.

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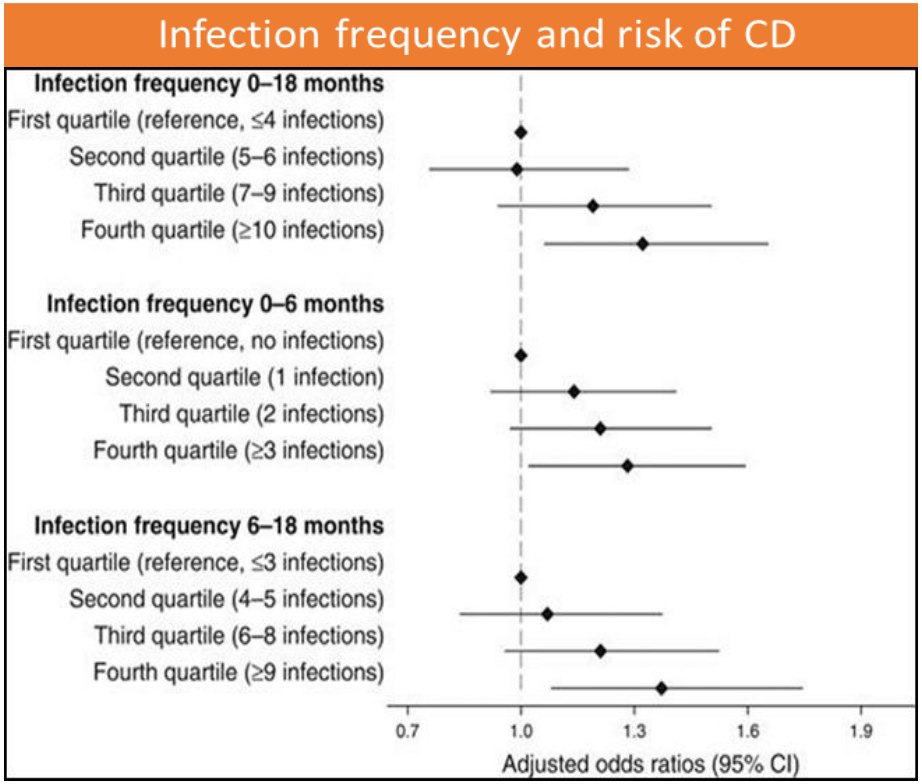
Infections

Infections and risk of coeliac disease in childhood: a prospective nationwide cohort study

Norwegian Mother and Child Cohort Study (MoBa)

Parent-reported infectious disease data 0-18 moths in 72,921 children born between 2000-2009:

- **Upper respiratory tract infection**: OR=1.03, 95%CI=1.02-1.05
- **Lower respiratory tract infection:** OR=1.12, 95%CI=1.01-1.23
- **Gastroenteritis**: OR=1.05, 95%CI=0.99-1.11
- **Number of infections:** ≥10 infections <18 months increased the risk of coeliac disease compared with ≤4 infections.



Conclusion: Early life infections may have a role in coeliac disease.

Mårild et al. Am J Gastroenterol. 2015 Oct;110(10):1475-84.

Factors that increase risk of coeliac disease autoimmunity after a gastrointestinal infection

The TEDDY study

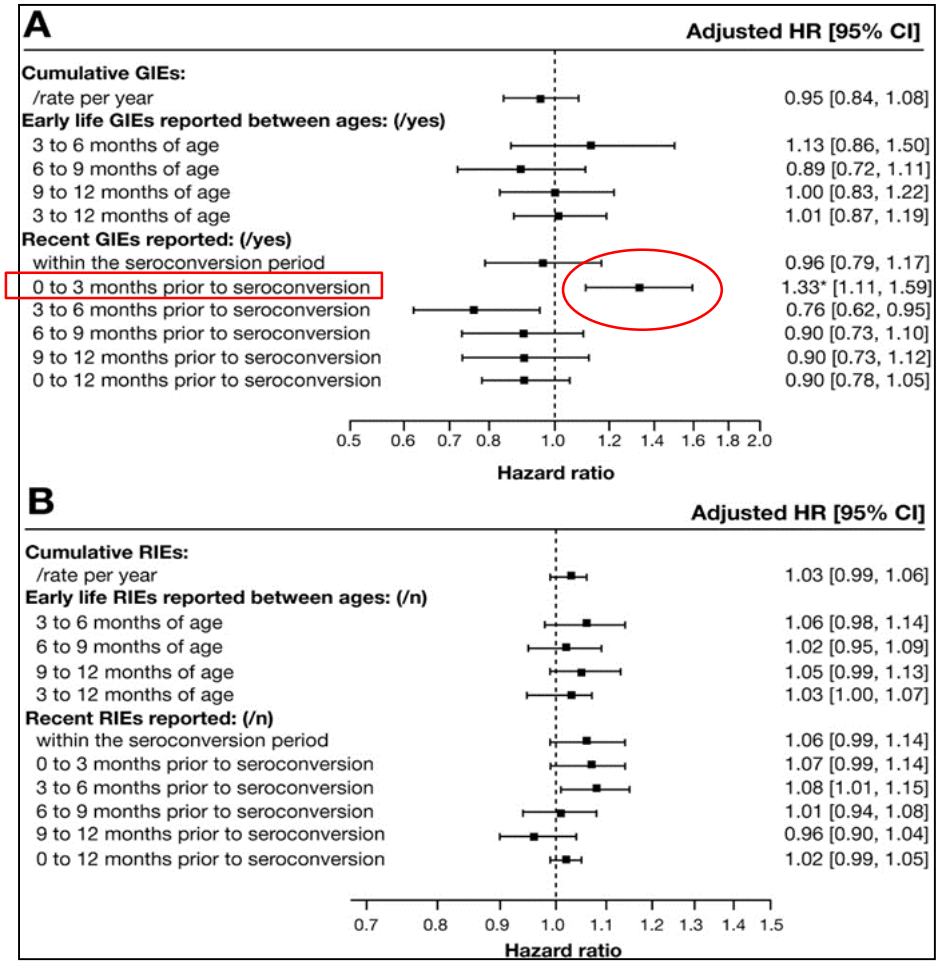
Parental reports of infections were collected from birth from 6,327 children between1-4 years of age:

- 13,881 gastrointestinal infectious episodes (**GIE**)
- 79,816 respiratory infectious episode (**RIE**) were identified.

- **GIE** (**A**) (but not RIE; **B**) increased the risk of CDA within the following 3 months by 33%.

Conclusion: GIEs increase the risk of coeliac disease autoimmunity.

Risk of CDA between 1-4 years of age for (A) GIEs and (B) RIEs



Kemppainen et al. Clin Gastroenterol Hepatol. 2017 May;15(5):694-702.

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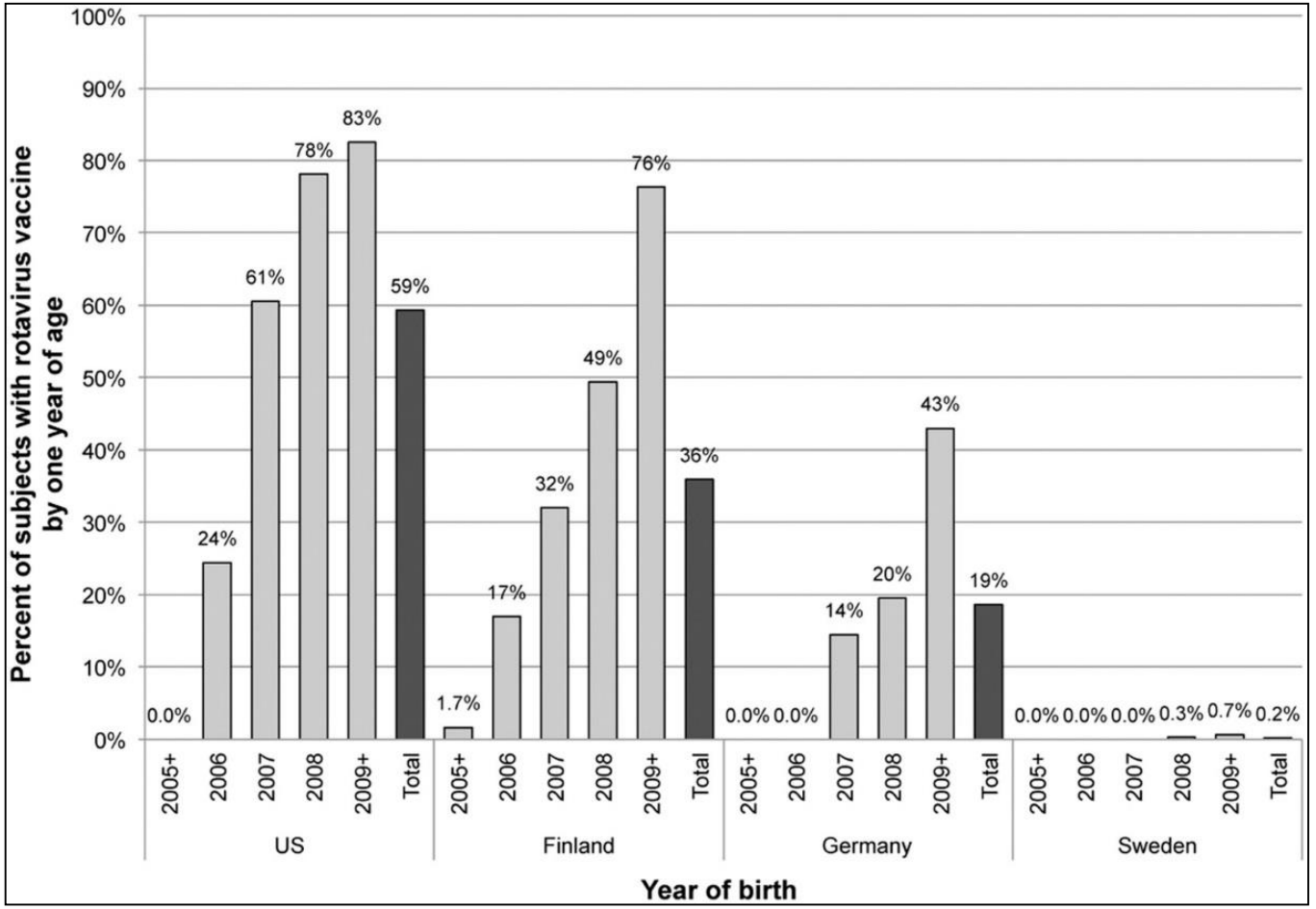
Rotavirus vaccination coverage by Country



Kemppainen et al. Clin Gastroenterol Hepatol. 2017 May;15(5):694-702.

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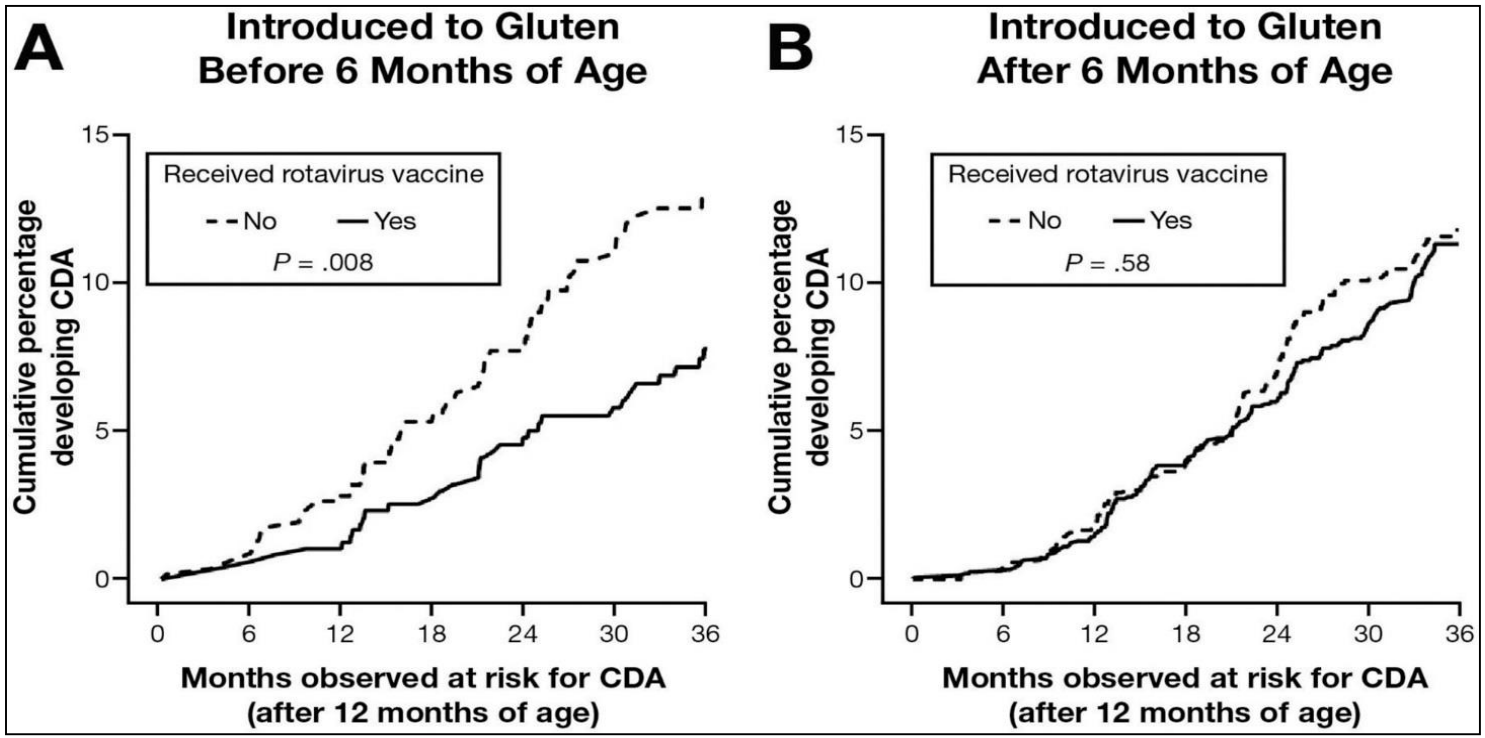
Rotavirus vaccination and gluten introduction

Kaplan–Meier curves of CDA by rotavirus vaccine separately for children introduced to gluten (*A*) before 6 months of age or (*B*) after 6 months of age.



Conclusion: Viruses, especially rotavirus, may act as a trigger in early life and the risk is modified further by when gluten is introduced.

Kemppainen et al. Clin Gastroenterol Hepatol. 2017 May;15(5):694-702.

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Mode of delivery

Pregnancy outcome and risk of coeliac disease in offspring: a nationwide case-control study

Pregnancy data from the Swedish Medical Birth Register

- Pregnancy data 1973 - 2008 from 11,749 offspring with coeliac disease and 53,887 matched controls from the general population.
- **No increased risk of coeliac disease after emergency** (OR=1.02; 95%CI=0.92-1.13) **or any caesarean section** (OR=1.06; 95%CI=0.99-1.13).
- **Elective caesarean section** was associated with coeliac disease (OR=1.15; 95%CI=1.04-1.26).

Risk of Celiac Disease After Cesarean Delivery

Mode of delivery:	Controls (%)	CD (%)	OR (95%CI)	*P*
• Cesarean section	5766/53,887 (10.7)	1299/11,749 (11.1)	1.06 0.99–1.13	0.074
• Emergency section	2136/41,699 (5.1)	444/8827 (5.0)	1.02 0.92–1.13	0.749
• Elective section	2125/41,688 (5.1)	508/8891 (5.7)	1.15 1.04–1.26	0.005

Conclusion: Bacterial flora of the newborn plays a role in coeliac disease.

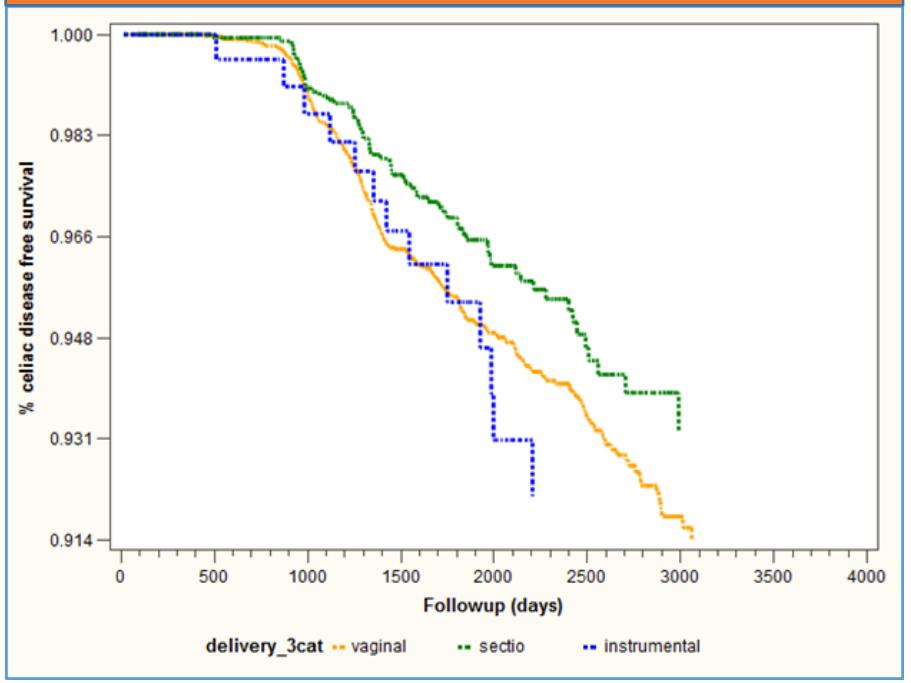
Mårild et al. Gastroenterology. 2012 Jan;142(1):39-45.e3.

Caesarean section on the risk of coeliac disease in the offspring

The TEDDY study

- 1600 of 6,087 singletons (26%) born by C-section, 4487 (74%) vaginally without instrumental support. Of those, 343 (6%) developed coeliac disease.
- **No association** with CDA (HR = 0.91, 95%CI=0.78-1.06, p = 0.20) and CD (HR = 0.85, 95%CI=0.65-1.11, p = 0.24).
- Pre-surgical ruptured membranes had no influence on CDA or CD development.

Kaplan-Meier plot for coeliac disease by delivery mode



Conclusion: C-sections do not increase the risk of coeliac disease.

Koletzko et al. J Pediatr Gastroenterol Nutr. 2018 Mar;66(3):417-424.

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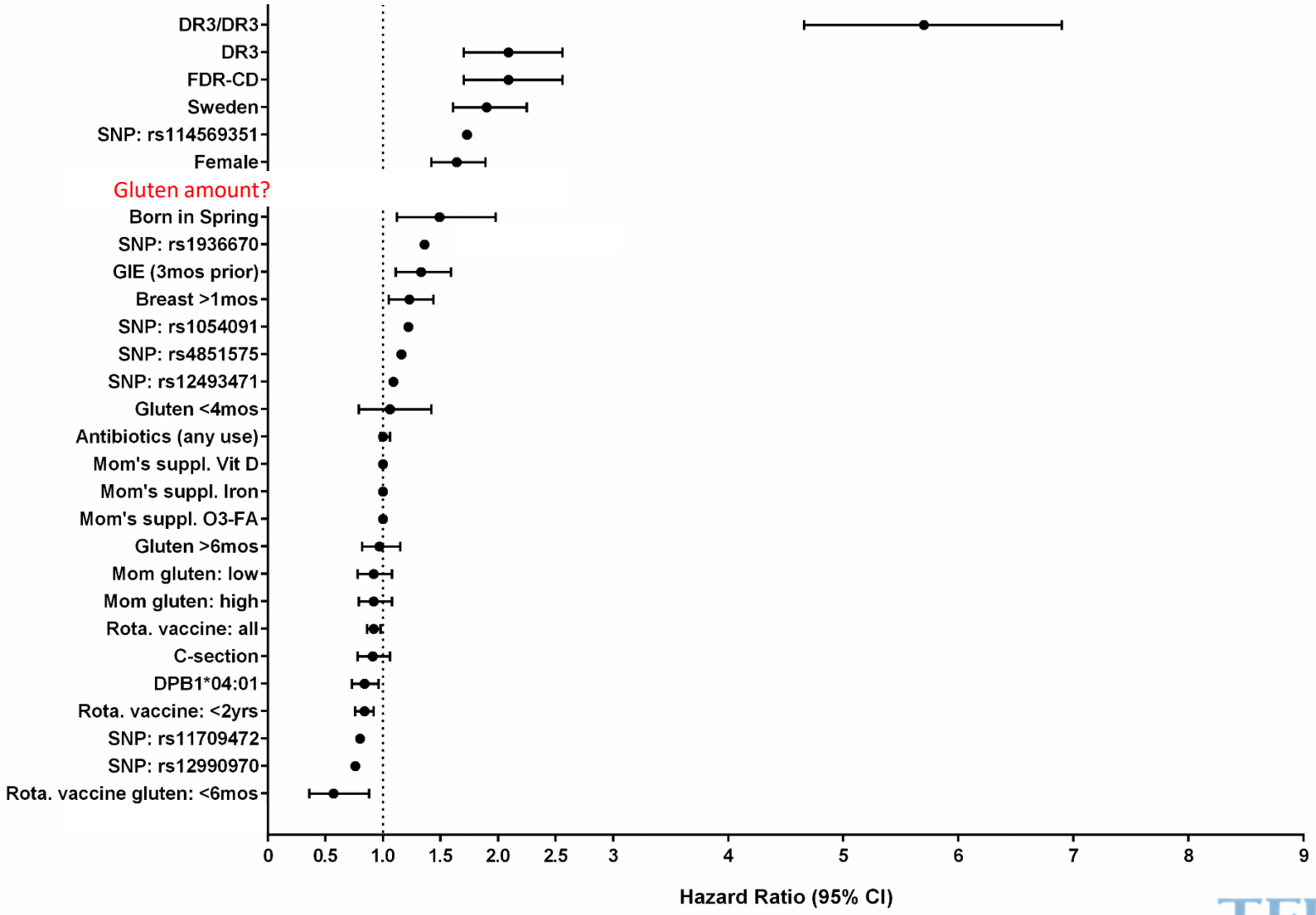
Summary from TEDDY
…this far

Associated risk factors in TEDDY



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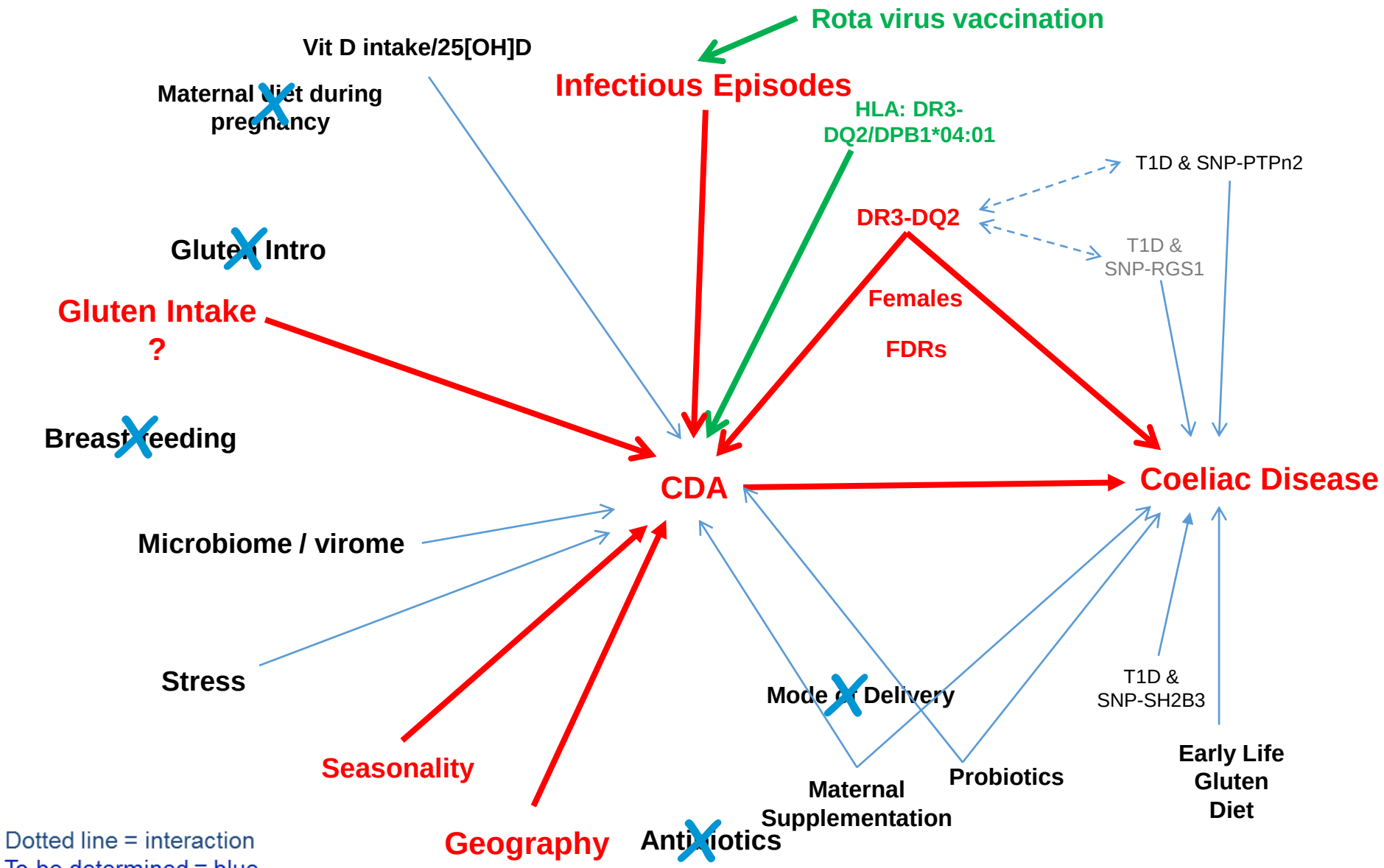

CDA, coeliac disease autoimmunity.

Take home message from TEDDY

Role of HLA:

- HLA-DQ2/DQ2 is the strongest risk factor in paediatric coeliac disease.
- Other risk factors are female gender and having family history of coeliac disease, indicating the importance of genetics.

Role of the diet:

- Time to first introduction of gluten or breastfeeding are *not* associated with paediatric coeliac disease.
- High intake of gluten amounts may increase the risk (at last in Swedish children).
- Gluten intake on the risk of coeliac disease needs to be confirmed in all TEDDY.

Role of infections:

- Early life infections may play a role, especially a gastrointestinal infection.
- Multiple infections increase the risk.
- The protective effect of rotavirus vaccination indicate a role of a virus.

Role of mode of delivery (as proxy for change in microbiome):

- Mode of delivery is not associated (risk of bias in register studies).

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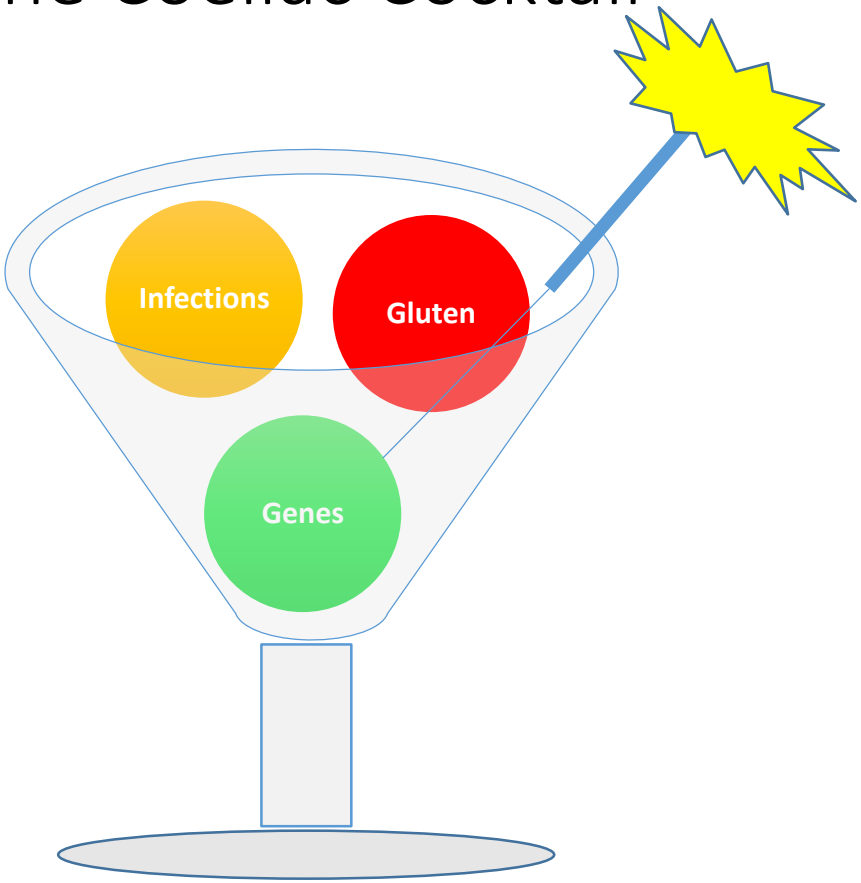
The Coeliac Cocktail



Prospective data makes it possible to study the interaction!

Happy anniversary, from the TEDDY Study Group!

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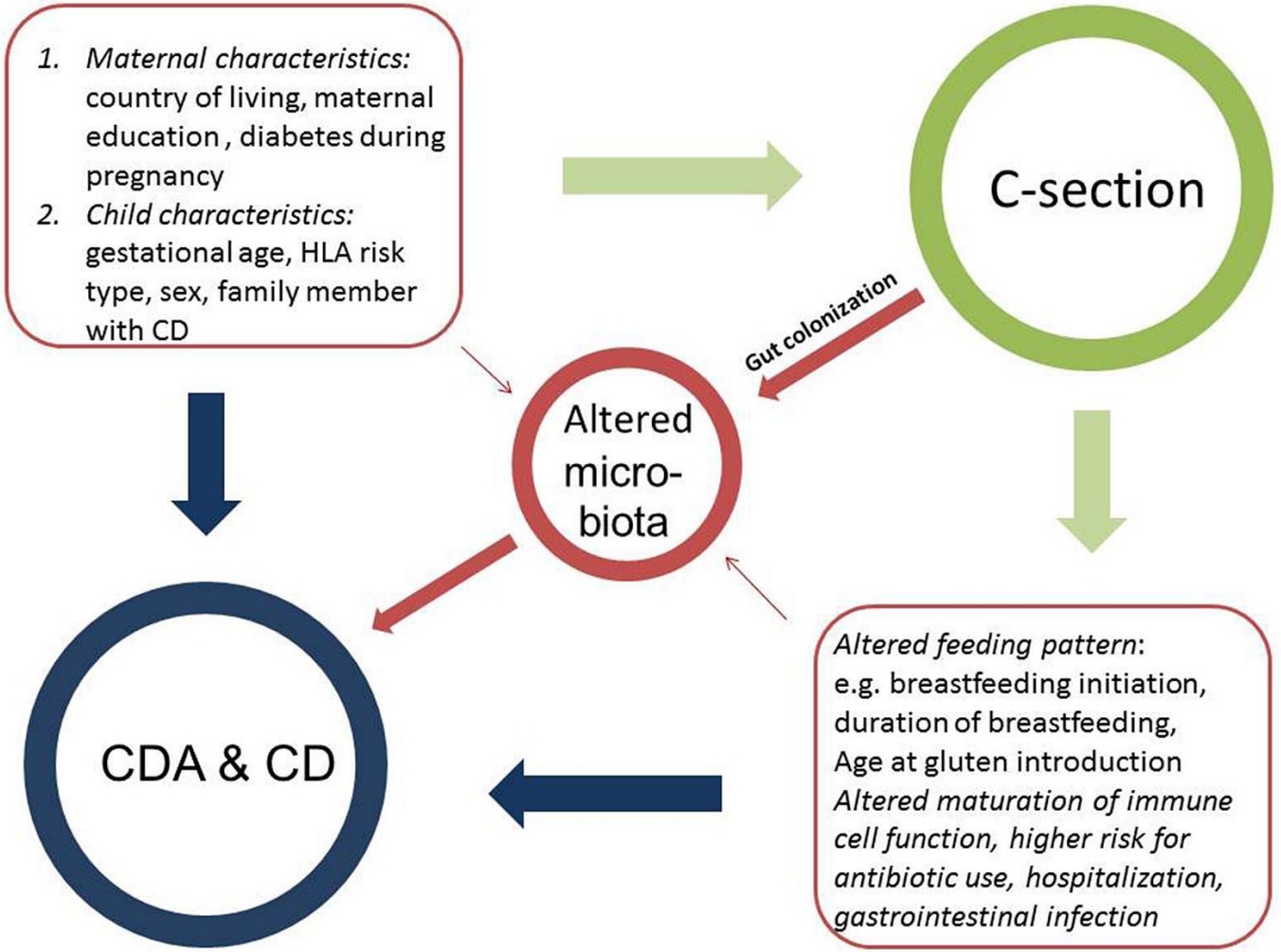
Interactions of maternal & child characteristics, infections, mode of delivery, infant feeding, antibiotics and microbiome



Koletzko et al. Cesarean Section on the Risk of Celiac Disease in the Offspring: The Teddy Study. J Pediatr Gastroenterol Nutr. 2018 Mar;66(3):417-424.

Influence of the ‘environment’

The Karelia study

Type 1 diabetes is 6-fold lower in Russian Karelia than in Finland, despite no differences in frequency of predisposing HLA-DQ genotypes in the background populations.

Kondrashova et al. Ann Med. 2005;37(1):67-72.

Coeliac autoimmunity is more than 2-fold less frequent in Russian Karelia than in Finland (0.6% versus 1.4%, P=0.005).

Kondrashova et al. Ann Med. 2008;40(3):223-31