

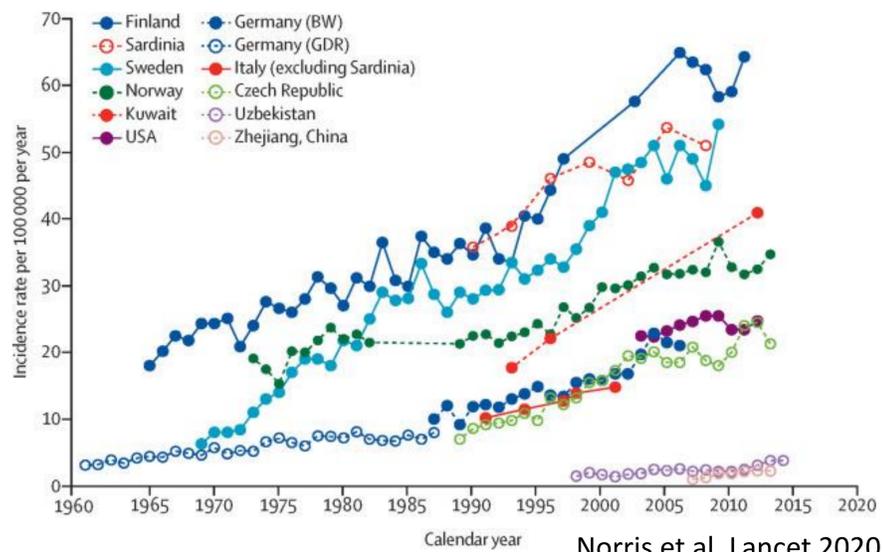
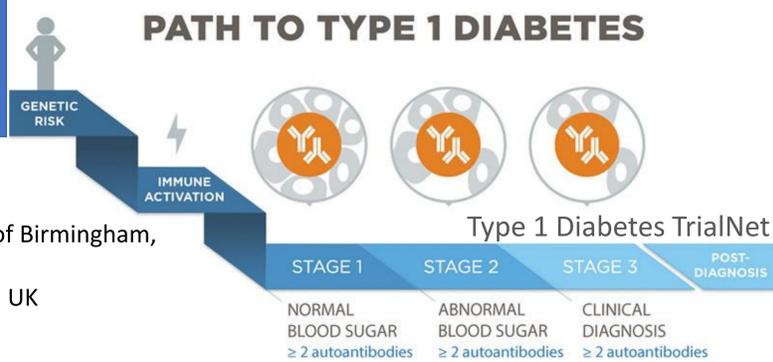
Review: Environmental determinants of type 1 diabetes

-> From association to causality

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[1] Background

The rising incidence of type 1 diabetes (T1D) cannot be ascribed to genetics alone, and causative environmental triggers and drivers must also be contributing [1-3].

[2] Aims

This narrative review outlines the evidence to date to support the pathways from association to causality, across all stages of T1D (seroconversion to beta cell failure).

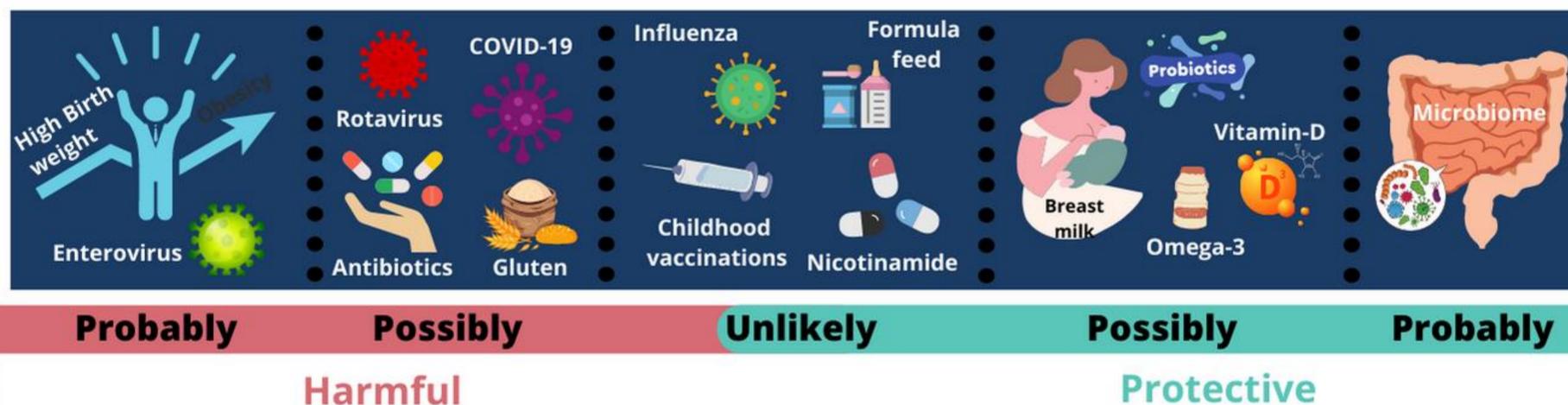
[3] Methods

We undertook this review through searching PubMed and Medline. We included systematic reviews, meta-analyses, RCT, cohort studies (prospective and retrospective) and case-control studies. Reference lists were screened for relevant articles.

We focus on:

1. Infections and vaccinations
2. Birthweight, infant growth and obesity
3. Gut microbiome

Likelihood of causal association



Class of agent	Agent	Current strength of association with IA or T1D	Proving contribution to causality
Infections and vaccinations	Enterovirus	Probable	Vaccination trials in planning
	Rotavirus	Possible	Rotavirus vaccinations being incorporated into childhood vaccination programmes in some countries
	Influenza	Unlikely	Studies show inconsistent results
	COVID-19	Possible	Vaccination programmes being set up
	Childhood vaccinations	Unlikely	Studies show inconsistent results
Weight	Birthweight	Probable	RCT and intervention studies needed
	Infant growth	Probable	RCT and intervention studies needed
	Childhood obesity	Probable	RCT and intervention studies needed
The Gut	Microbiome	Probable	RCT needed
	Breastfeeding	Possible	RCT evidence supports no role
	Cow's milk/formula feeds	Unlikely	RCT evidence supports no role
	Gluten	Possible	Studies show inconsistent results
	Antibiotic use	Possible	Studies show inconsistent results
	Probiotic use	Possible	RCT evidence supports no role but small study
	Vitamin D	Possible	Conflicting RCT results of vitamin D supplementation
	Nicotinamide	Unlikely	RCT evidence supports no role
	Omega-3 (PUFA)	Possible	Conflicting RCT results of PUFA supplementation

[4] Key messages:

Despite over 40 years of investigation, with multiple, international case-control, cohort, and prospective studies, we are still in search of those critical environmental triggers for T1D [1-3].

The TEDDY study has provided the largest evaluation of environmental triggers in genetically predisposed children to date [4]. Lessons learned are that T1D is a highly heterogeneous condition, influenced by both genetic [1] and environmental factors [2], which interact through the threshold hypothesis [5], to initiate and promote T1D over time.

We would suggest a way forward for this field is first to explore and establish the environmental factors that associate with risk for IA and/or T1D. Once identified, these can be tested, ideally through RCT.

[5] References:

1. Pociot F, Lernmark A. Genetic risk factors for type 1 diabetes. *Lancet*. 2016;387(10035):2331-9
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5. Wasserfall C, Nead K, Mathews C, Atkinson MA. The threshold hypothesis: solving the equation of nurture vs nature in type 1 diabetes. *Diabetologia*. 2011;54(9):2232-6.
6. Dedrick S, Sundaresh B, Huang Q, Brady C, Yoo T, Cronin C, et al. The Role of Gut Microbiota and Environmental Factors in Type 1 Diabetes Pathogenesis. *Front Endocrinol (Lausanne)*. 2020;11:78.
7. Boddu SK, Aurangabadkar G, Kuchay MS. New onset diabetes, type 1 diabetes and COVID-19. *Diabetes Metab Syndr*. 2020;14(6):2211-7.



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