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Cow's milk allergy in infancy and later development of type 1 diabetes–nationwide case-cohort study

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Abstract

Bakground: It is suggested that early intake of cow's milk could be a risk factor for type 1 diabetes (T1DM). Further, the different immunological background, gives a suggestion of an inverse relationship for the occurrence of these diseases. The aim of this study was to explore the association between cow's milk allergy (CMA) and the risk of T1DM in a register-based case-cohort study.

Methods: Data were obtained from Finnish nationwide health registers. The study included all children born in Finland between January 01, 1986 and December 31, 2008 and diagnosed with T1DM before the age of 16 years (n = 7754). A 10% random sample from each birth year cohort was selected as a reference cohort (n = 137,798). T1DM, CMA, and asthma were defined based on valid special reimbursements for the costs of drugs/special formulas needed in the treatment of the diseases. Child's sex, birth decade, asthma, maternal diabetes and asthma, smoking during pregnancy, and previous deliveries were considered as confounding factors. Time-dependent, weighted Cox regression was applied for statistical analyses.

Results: Children with CMA had an increased risk of developing T1DM in fully adjusted model (HR = 1.17; 95% CI 1.02–1.34), but the association was no longer observed when including the use of special infant formulas in the definition of CMA in the sensitivity analysis (HR = 1.11; 95% CI 0.92–1.32). CMA was associated with an increased risk of T1DM in children without asthma (HR = 1.27; 95%CI 1.10–1.47), but not in children with asthma (HR = 0.80; 95% CI 0.92–1.27).

Conclusion: Children with CMA may have an increased risk of T1DM.

KEYWORDS
child, cohort studies, diabetes mellitus type 1, milk, milk hypersensitivity

1 | INTRODUCTION

In Finland, the incidence of type 1 diabetes (T1DM) as well as the prevalence of cow's milk allergy (CMA) under the age of 5 years are one of

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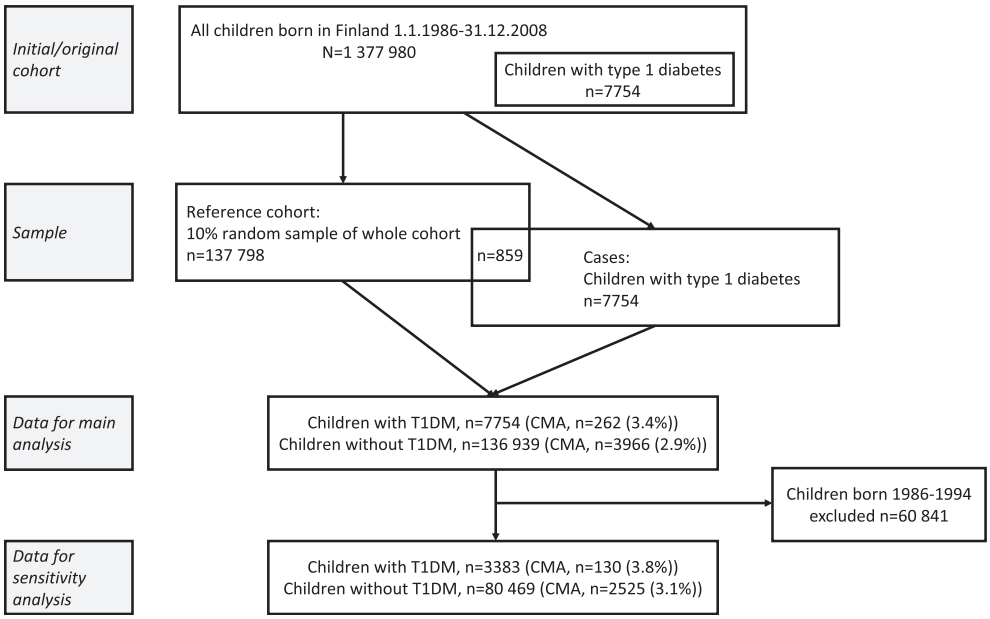

FIGURE 1 Flowchart of the participants. T1DM, type 1 diabetes; CMA, cow's milk allergy

the highest in Europe.[1,2] There are at least two background factors that connect these conditions, immunology and cow's milk.

The immunological reactions behind T1DM and allergic diseases are different and to some extent opposite. The autoimmunity process in T1DM involves T-helper type 1 cells (Th1) and Th17, whereas the allergic inflammation is characterized by Th2 immune response. Based on the reciprocal counter-regulation between Th1 and Th2 cells,[3] the Th1/Th2 paradigm suggests an inverse relationship between autoimmune and allergic diseases. In the meta-analysis of observational studies, the inverse association between T1DM and allergic diseases was only observed for asthma, but not for allergic rhinitis or atopic dermatitis. Further, for each outcome the individual studies reported null, direct and inverse associations.[4] For food allergies, both direct[5] and null[6] associations have been reported, suggesting that the Th1/Th2 paradigm might be an oversimplification.

On the other hand, early cow's milk exposure has been suggested to play a role in the development of T1DM.[7-9] Findings from prospective cohort studies are consistent in that cow's milk intake during childhood is directly associated with development of pre-T1DM and/or T1DM in children.[10-14] However, the age at introduction of cow's milk during infancy does not seem to be associated with T1DM risk.[15-18] A randomized trial found no reduction in the risk for T1DM in the 11.5 years follow-up time when comparing weaning to an extensively hydrolyzed infant formula with weaning to a commercial cow's milk-based formula during the first 6–8 months of life (HR 1.1 95% CI 0.8–1.5).[19] However, a recent finding from a prospective cohort study suggests that early feeding of extensively hydrolyzed formula is directly associated with pre-T1DM.[15] Based on the current evidence, the role of CMA or the early use of cow's milk in development of T1DM remains unclear. Further, to best of our knowledge, the association between CMA and T1DM has not been reported before.

The aim of this study was to examine the association between CMA and the risk of T1DM in a case-cohort study design using Finnish nationwide registers. Based on the Th1/Th2 paradigm and the cow's milks suggested role as a risk factor for T1DM, we hypothesized that children with CMA have a decreased risk for developing T1DM.

2 | MATERIALS AND METHODS

2.1 | Data sources and study population

The data for the present study were collected from four nationwide registers: the Population Register, the Special Reimbursement Register (information on special reimbursement for insulins available since 1964, and for special infant formulas since 1986), and the Drug Prescription Register (available since 1994) maintained by the Social Insurance Institute of Finland, and the Medical Birth Register (available since 1987), maintained by the Finnish Institute for Health and Welfare. The unique personal identity codes included in all registers were used to link, the information from different registers.[20]

The initial cohort included all children born in Finland between January 1, 1986 and December 31, 2008 (n = 1,377,980). From this initial birth cohort, we identified all children with T1DM before the age of 16 years or the end of year 2009 as cases from the Special Reimbursement Register (n = 7754). For a reference cohort, we selected a 10% random sample for each initial birth year cohort from the Population Register (n = 137,798). Due to the study design, altogether 859 children with T1DM were also included in this random sample and thus included in the reference cohort (Figure 1).

2.2 | Definition of T1DM and CMA

We defined T1DM and CMA based on the information about the valid special reimbursement for the costs of insulins or special infant formulas needed in the treatment of these diseases. This information was

obtained from the Special Reimbursement Register maintained by the Social Insurance Institute. In Finland, this special reimbursement is granted by the Social Insurance Institute based on a written statement by a physician describing the individual course of the disease and the diagnostic protocol. For each disease there are specific medical criteria defined by the Social Insurance Institute. To evaluate the fulfillment of these criteria, a clinical specialist in the Social Insurance Institute further assesses the physician's statement. The admittance for the special reimbursement is not dependent of the child's place of residence, socioeconomic status or place of treatment. From the register we extracted information about the start and end date of the special reimbursements and the Social Insurance Institute's disease code. The date of admittance of the special reimbursement was used as a proxy for the date of diagnosis. T1DM was defined as a valid special reimbursement and at least one insulin (Anatomical Therapeutic Chemical [ATC] code A10) purchase after the special reimbursement.

We considered CMA as the exposure disease. In Finland, the special reimbursement for special infant formulas is granted for children with CMA up to age of 2 years. During the observation period The Social Insurance Institute criteria for this special reimbursement included a clinical examination by a pediatrician and disappearance of symptoms suggestive for CMA during the elimination diet for cow's milk. In addition, either positive skin prick test for cow's milk protein or elevated cow's milk protein specific serum IgE-value or positive oral food challenge was required. At the time, the double-blind, placebo-controlled food challenge was not required. Instead, for the majority of children the diagnosis was based on open food challenge.[21]

Our main definition for CMA was a valid special reimbursement for special infant formulas at least for 6 months. As this definition is potentially open to false positive diagnosis, we also used a strict CMA definition where at least three special infant formula purchases after the special reimbursement were required.

In Finland, the drugs and special infant formulas are sold exclusively from pharmacies and the drugs are dispensed on prescription only. From the Drug Prescription Register we collected the information of the date of purchase and for drugs the ATC code (insulins (ATC code A10) and anti-asthmatic drugs (ATC code R03)) and for special infant formula the product code. The Drug Prescription Register has recorded all reimbursable purchases since 1994.

2.3 | Confounding factors

The information on maternal age at delivery, smoking during pregnancy, socioeconomic status, the number of mother's previous deliveries, mode of delivery, as well as gestational age, child's birth year, sex, birth weight and birth length were derived from the Medical Birth Register. Additionally, the information on maternal asthma and diabetes were collected from the Special Reimbursement Register.

Based on our recent findings on increased risk of T1DM in children with asthma[22] and in children using anti-asthmatic drugs,[23] we considered child's asthma as a potential confounding factor with three different definitions. Our main definition for asthma was a valid special reimbursement for the costs of anti-asthmatic drugs, data obtained from the Special Reimbursement Register. The criteria by the Social Insurance Institute for this special reimbursement is that the asthma diagnosis is made based on either pulmonal function tests showing obstruction or recurrent obstructive episodes verified by pediatrician and the need of long-lasting drug therapy with inhaled corticosteroids. As this definition likely excludes children with only mild asthma or only intermittent drug treatment, we used two additional, more wider definitions in the sensitivity analyses: (1) a valid special reimbursement for asthma or at least one purchase of any anti-asthmatic drug (ATC code R03) without the special reimbursement, and (2) at least one purchase of any anti-asthmatic drug (ATC code R03).

2.4 | Statistical analysis

To analyze the association between CMA and the risk of T1DM we used a weighted Cox proportional hazard regression using inverse probability weighting to account for the case-cohort design. We considered CMA and asthma as time-dependent variables and the start date of the special reimbursement or the date of the first purchase of any anti-asthmatic drug were used as a proxy for the start of the disease. We followed-up the study population until the appearance of T1DM, age of 16 years, end of year 2009, or death whichever came first. We estimated unadjusted, partially adjusted, and one fully adjusted model. The fully adjusted model included the information of child's sex, birth decade and asthma as well as maternal asthma, diabetes, smoking during pregnancy, and number of previous pregnancies. These variables were selected based on previous knowledge and their associations with T1DM and CMA in the present data.[24-26] These analyses were considered as the main analyses.

We conducted multiple sensitivity analyses in a subgroup of children born 1995–2008, as the information on drug and special infant formula purchases were available since 1994. First, we repeated the main analyses to evaluate the potential effect of a smaller sample size. Second, we conducted the analyses using the strict CMA definition to evaluate the potential misclassification of CMA. Third, we conducted analyses using the two additional definitions for asthma.

To examine whether the association between CMA and the risk of T1DM was modified by child's asthma, an interaction term between CMA and asthma was included in the models. Missing data were handled by complete case analysis. Analyses were performed using STATA, version 14, (RRID:SCR_012763) software.

2.5 | Ethical approval

The Institutional Review Board of the Finnish Institute for Health and Welfare, and the institutions keeping the registers, after hearing The National Data Protection Authority, have approved the study.

TABLE 1 The characteristics of the study population

Characteristics	Children with T1DM (*n* = 7754); *n* (%)	Children without T1DM (*n* = 136,939); *n* (%)
Mean follow-up time (years), mean (SD)	7.4 (4.1)	11.2 (5.0)
Male sex	4226 (55)	70,059 (52)
Child's birth year		
1986–1989	1821 (23.5)	24,351 (17.8)
1990–1999	4610 (59.5)	61,388 (44.8)
2000–2008	1323 (17.1)	51,200 (37.4)
Child's asthma	564 (7.3)	7141 (5.2)
Child's cow's milk allergy	262 (3.4)	3966 (2.9)
Gestational age in weeks		
<37	452 (5.8)	7103 (5.2)
37–41	6519 (84.1)	116,887 (85.4)
≥42	292 (3.8)	6087 (4.5)
Missing information	491 (6.3)	6862 (5.0)
Maternal age at delivery (years), mean (SD)	29.5 (5.1)	29.6 (5.3)
Maternal smoking during pregnancy		
No	6251 (81)	107,448 (78)
Yes	856 (11)	20,056 (15)
Missing information	647 (8.3)	9435 (6.9)
The number of previous deliveries		
0	2976 (38)	53,262 (39)
1	2570 (33)	44,133 (32)
≥2	1722 (22)	32,874 (24)
Missing information	486 (6.3)	6670 (4.9)
Mode of delivery		
Vaginal	6013 (77.6)	109,688 (80.1)
Cesarean section	1274 (16.4)	20,864 (15.2)
Missing information	467 (6.0)	6387 (4.7)
Maternal socioeconomic status		
Upper-white collar	872 (11.3)	15,779 (11.5)
Lower-white collar	2542 (32.8)	39,255 (28.7)
Blue collar	891 (11.5)	15,825 (11.6)
Others	863 (11.1)	16,936 (12.4)
Missing information	2586 (33.3)	49,144 (35.8)
Maternal diabetes	184 (2.4)	557 (0.41)
Maternal asthma	221 (2.9)	3802 (2.8)

3 | RESULTS

We identified 7754 children with T1DM, and our reference cohort consisted of 137,798 children. The mean follow-up time for children with T1DM was 7.4 years (SD 4.1) and for children without T1DM 11.2 years (SD 5.0). Altogether we identified 4228 children with CMA, diagnosed at the mean age of 7.1 months (SD 3.9). For all children with both CMA and T1DM (*n* = 262), CMA was diagnosed before T1DM, with the CMA diagnosed at the mean age of 7.2 months (SD 4.2). The children with T1DM were more often male, had asthma, and more often their mothers had diabetes, were non-smokers during pregnancy, and had fewer previous pregnancies (Table 1). Children with CMA were more often male (58% vs. 51%) and had asthma (19% vs. 5%) and more often their mothers were non-smokers (87% vs. 78%) and had asthma (6% vs. 3%).

In our main analyses in the children born between 1986 and 2008, CMA was associated with an increased risk of T1DM in unadjusted analysis (HR = 1.29; 95% CI 1.13–1.46) and the increased risk remained in the fully adjusted model including the child's sex, birth decade, and asthma as well as maternal asthma, diabetes, smoking during pregnancy, and number of previous pregnancies (HR = 1.17; 95% CI 1.02–1.34) (Table 2).

In the sensitivity analysis we repeated the main analysis among children born between 1995–2008 and the association between CMA and T1DM was present in the unadjusted model, but no longer in the fully adjusted model (HR = 1.12; 95% CI 0.94–1.33) (Table 2). When further using the strict CMA definition, these results did not change substantially (Table 2). Similarly, when using the two additional definitions for asthma as a confounding factor and the main CMA definition, the results were not substantially different (a valid special reimbursement or at least one purchase of any anti-asthmatic drug: full adjusted HR = 1.14: 95% CI 0.96–1.35, at least one purchase of any anti-asthmatic drug: full adjusted HR = 1.14; 95% CI 0.96–1.35).

We observed an interaction between child's CMA and asthma (p for interaction = 0.002). In the separate analyses according to asthma, we observed that CMA was associated with an increased risk of T1DM in children without asthma (HR = 1.27; 95%CI 1.10–1.47), but not in children with later asthma (HR = 0.80; 95% CI 0.92–1.27) when adjusted for child's sex, birth decade, maternal asthma, diabetes, smoking during pregnancy, and number of previous pregnancies.

4 | DISCUSSION

In the present study, we showed that CMA was associated with an increased risk of T1DM after adjusting for several potential confounding factors. However, when applying stricter CMA criteria, the association between CMA and the risk of T1DM was no longer observed.

The major strength of our study is the use of nationwide register-based data with a good coverage. Further, the prospectively collected information and the relatively large number of cases minimize the recall bias. In addition, our criteria for T1DM should be reliable, because the criteria for the special reimbursement is evaluated by two independent specialists and the admittance is not dependent of the patient's socioeconomic status or the place of residence/treatment. Although the criteria for admittance are same for all types of diabetes in need of insulin, to our knowledge, the use of insulin is rare for types other than T1DM in children under 16 years of age.[27,28] Thus, the misclassification of cases should be minor. Other

TABLE 2 The main results of the association between CMA and the development of T1DM in children born in Finland between 1986 and 2008 and the results of the sensitive analysis of children born between 1995 and 2008 in a register based case-cohort study

	Children born in 1986–2008; *n* = 144,693 (T1DM *n* = 7754)		Children born in 1995–2008; *n* = 83,852 (T1DM *n* = 3383)			
	CMA[a] (*n* = 4228)		CMA[a] (*n* = 3065)		CMA[b] (*n* = 2665)	
	HR	95% CI	HR	95% CI	HR	95% CI
Unadjusted	1.29	1.13–1.46	1.21	1.02–1.43	1.20	1.00–1.43
Adjusted for sex and birth decade	1.25	1.09–1.42	1.20	1.02–1.42	1.19	0.99–1.42
Adjusted for sex, birth decade, asthma	1.18	1.04–1.35	1.16	0.98–1.38	1.15	0.96–1.38
Adjusted for sex, birth decade, asthma, maternal asthma and diabetes, smoking during pregnancy, number of previous deliveries	1.17	1.02–1.34	1.12	0.94–1.33	1.11	0.92–1.32

Abbreviations: CMA, cow's milk allergy; T1DM, type 1 diabetes.
[a]CMA defined based on a valid special reimbursement for at least 6 months.
[b]CMA defined based on a valid special reimbursement for at least 6 months and at least three formula purchases from the pharmacy.

strengths include our possibility to take into account several potential confounders, including two new, recently identified factors: child's asthma and child's use of anti-asthmatic drugs.[22,23] However, we may have missed some potentially important confounders, like diet and paternal factors,[8,29-31] thus the residual confounding cannot be ruled out.

A major limitation of the present study is that the definition for CMA may be open for misclassification of the children. Although it is possible that the child has been granted for the special reimbursement without an oral food challenge, in practice majority of the children diagnosed with CMA had undergone food challenge before the diagnosis.[21] During the observation period, the food challenge was usually done as open food challenge, which is further open for misclassification, especially for the non-IgE-mediated CMA for which the double-blind, placebo-controlled food challenge would be more accurate.[32] We tried to disentangle the potential misclassification by applying a strict CMA definition, which included also information on purchased special infant formulas. When using this strict CMA definition, the association between CMA and the risk of T1DM was no longer seen. However, these results were similar to those obtained from the models using the main CMA definition in the same birth year-restricted subgroup, indicating that the disappearance of the association might be because of smaller sample size rather than inaccuracy in definition of CMA. Further, we may have missed some children receiving the CMA diagnosis after the age of 1 year, because the special formula is possible to be replaced by other milk substitutes after the age of 1 year. However, for majority of the children the symptoms start rapidly after the first exposure for cow's milk formula and thus the appearance of CMA after the age of 1 year is rare.[33,34] In addition, the prevalence of CMA in children without T1DM was approximately 3% regardless of used definition for CMA, which is similar in comparison to previously reported prevalence in Finland.[35-37] Thus, we consider that the probable inaccuracy in the definition of CMA did not cause major bias to our study. Because of the high incidence of T1DM in Finland, the generalizability of our results to pediatric populations with low incidence of T1DM calls for precaution.

To best of our knowledge, the association between CMA and T1DM has not been reported before. Further, studies concerning the coexistence of any/other food allergies and T1DM are scarce, and both increased risk for T1DM[5] and null associations have been reported.[6] For other allergic diseases, like atopic eczema, more studies exists and both direct[38] and inverse[39,40] as well as null associations[41,42] have been reported.

As the results from studies concerning the coexistence of allergic diseases and T1DM are scarce it is suggested that the Th1/Th2 paradigm might be an oversimplification, which is supported by our results as well. After the introduction of this original paradigm other kinds of Th-cells, including Th17 cells, have been recognized[43] .Thus, the immunopathology behind these diseases might be more complex than previously thought.

In Finland the special reimbursement for special infant formula correlates well with the strict cow's milk elimination diet.[44] Therefore our finding about the possible co-occurrence of CMA and T1DM does not support the previous findings about the direct association between childhood cow's milk consumption and the development of T1DM and prevention of T1DM by eliminating cow's milk from infants diet.[8,9] Our result is rather supported by a recent RCT, which did not observe any difference in the development of T1DM related autoantibodies nor T1DM when comparing groups weaned either extensively hydrolyzed infant formula or commercial formula.[19]

Our observation of the possible co-occurrence of CMA and T1DM might be explained by the shared risk factors behind the diseases. The increased prevalence of autoimmune and allergic diseases in western countries have been explained by the decrease in number of infectious diseases and microbial exposures.[45] In addition, previous studies have observed that these changes in environmental factors may alter the diversity of gut microbiota, which may lead to adverse immunological reactions.[46] For both, T1DM and CMA, studies have reported that changes in the gut microbiota, leading to dysbiosis, could be involved in the development of the diseases.[47,48] Furthermore, the gut microbiota of children with CMA is observed to differ before and after the cow's milk protein elimination when compared to healthy controls.[49] These changes in gut microbiota, reflecting the

western lifestyle or the elimination of cow's milk protein from diet, may at least partly explain our result of the direct association between CMA and the risk T1DM.

We observed that CMA was associated with an increased risk of T1DM in children without asthma, but not in children with later asthma. The meta-analysis have observed a slight inverse association between asthma and T1DM,[4] however individual studies are reporting all inverse, diverse and null results.[50] Further, we have recently reported that the direction of the association between asthma and T1DM in childhood is dependent by the sequential appearance of the diseases: prior diagnosed asthma increased the risk of subsequent development of T1DM, but prior T1DM decreased the subsequent development of asthma.[22] Also, we have reported that the use of anti-asthmatic drugs increased the risk of development of T1DM, thus the medication may have a role in the association between these diseases.[23] The explanation behind our finding is not clear, but at least it suggests that in future the asthma should be taken into account when studying the association between CMA and T1DM.

In conclusion, our results suggest that children with CMA may have an increased risk of T1DM. This finding supports that the Th1/Th2 paradigm might be oversimplification. Further, it is possible that dietary factors related to CMA, elimination of cow's milk or use of special infant formula in early childhood, may have a role in development of T1DM, but further studies are needed to confirm this.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Suvi M. Virtanen and Annamari Lundqvist designed the initial case-cohort setting. Suvi M. Virtanen, Annamari Lundqvist, Johanna Metsälä, Lauri J. Virta, Minna Kaila and Mika Gissler contributed to the planning of the data collection. Johanna Metsälä and Suvi M. Virtanen planned and Johanna Metsälä performed the statistical analysis. Anni Lamminsalo wrote the first version of the manuscript. All authors contributed to interpretation of data, revised the article critically for important intellectual content, and approved the final version to be published.

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REFERENCES

1. Patterson CC, Harjutsalo V, Rosenbauer J, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. *Diabetologia*. 2019;62(3):408-417.
2. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69(8):992-1007.
3. Shah A. The pathologic and clinical intersection of atopic and autoimmune disease. *Curr Allergy Asthma Rep*. 2012;12(6):520-529.
4. Cardwell CR, Shields MD, Carson DJ, Patterson CC. A meta-analysis of the association between childhood type 1 diabetes and atopic disease. *Diabetes Care*. 2003;26(9):2568-2574.
5. Wahlberg J, Vaarala O, Ludvigsson J. ABIS study group. Asthma and allergic symptoms and type 1 diabetes-related autoantibodies in 2.5-yr-old children. *Pediatr Diabetes*. 2011;12(7):604-610.
6. Caffarelli C, Cavagni G, Pierdomenico R, Chiari G, Spattini A, Vanelli M. Coexistence of IgE-mediated allergy and type 1 diabetes in childhood. *Int Arch Allergy Immunol*. 2004;134(4):288-294.
7. Kagohashi Y, Otani H. Role of nutritional factors at the early life stages in the pathogenesis and clinical course of type 1 diabetes. *Biomed Res Int*. 2015;2015:382165.
8. Virtanen SM. Dietary factors in the development of type 1 diabetes. *Pediatr Diabetes*. 2016;17(Suppl 22):49-55.
9. Gerstein HC. Cow's milk exposure and type I diabetes mellitus. A critical overview of the clinical literature. *Diabetes Care*. 1994;17(1):13-19.
10. Virtanen SM, Läärä E, Hyppönen E, et al. Cow's milk consumption, HLA-DQB1 genotype, and type 1 diabetes: a nested case-control study of siblings of children with diabetes. Childhood diabetes in Finland study group. *Diabetes*. 2000;49(6):912-917.
11. Virtanen SM, Hyppönen E, Läärä E, et al. Cow's milk consumption, disease-associated autoantibodies and type 1 diabetes mellitus: a follow-up study in siblings of diabetic children. *Diabet Med*. 1998;15(9):730-738.
12. Wahlberg J, Vaarala O, Ludvigsson J. ABIS-study group. Dietary risk factors for the emergence of type 1 diabetes-related autoantibodies in 21/2 year-old Swedish children. *Br J Nutr*. 2006;95(3):603-608.
13. Lamb MM, Miller M, Seifert JA, et al. The effect of childhood cow's milk intake and HLA-DR genotype on risk of islet autoimmunity and type 1 diabetes: the diabetes autoimmunity study in the young. *Pediatr Diabetes*. 2015;16(1):31-38.
14. Koivusaari K, Syrjälä E, Niinistö S, et al. Consumption of differently processed milk products in infancy and early childhood and the risk of islet autoimmunity. *Br J Nutr*. 2020;124:173-180. https://doi.org/10.1017/S0007114520000744.
15. Hummel S, Beyerlein A, Tamura R, et al. First infant formula type and risk of islet autoimmunity in the environmental determinants of diabetes in the young (TEDDY) study. *Diabetes Care*. 2017;40(3):398-404.
16. Virtanen SM, Kenward MG, Erkkola M, et al. Age at introduction of new foods and advanced beta cell autoimmunity in young children with HLA-conferred susceptibility to type 1 diabetes. *Diabetologia*. 2006;49(7):1512-1521.
17. Norris JM, Barriga K, Klingensmith G, et al. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. *JAMA*. 2003;290(13):1713-1720.
18. Chmiel R, Beyerlein A, Knopff A, Hummel S, Ziegler A-G, Winkler C. Early infant feeding and risk of developing islet autoimmunity and type 1 diabetes. *Acta Diabetol*. 2015;52(3):621-624.
19. Knip M, Åkerblom HK, Al Taji E, et al. Effect of hydrolyzed infant formula vs conventional formula on risk of type 1 diabetes. *JAMA*. 2018;319(1):38-48.
20. Gissler M, Haukka J. Finnish health and social welfare registers in epidemiological research. *Nor Epidemiol*. 2004;14:113-120.

21. Kaila M, Vanto T, Valovirta E, Koivikko A, Juntunen-Backman K. Diagnosis of food allergy in Finland: survey of pediatric practices. *Pediatr Allergy Immunol*. 2000;11(4):246-249.
22. Metsälä J, Lundqvist A, Virta LJ, et al. The association between asthma and type 1 diabetes: a paediatric case-cohort study in Finland, years 1981–2009. *Int J Epidemiol*. 2018;47(2):409-416.
23. Metsälä J, Lundqvist A, Virta LJ, et al. Use of Antiasthmatic drugs and the risk of type 1 diabetes in children: a Nationwide case-cohort study. *Am J Epidemiol*. 2020;189:779-787. https://doi.org/10.1093/aje/kwaa002.
24. Norris JM, Johnson RK, Stene LC. Type 1 diabetes—early life origins and changing epidemiology. *Lancet Diabetes Endocrinol*. 2020;8(3):226-238.
25. Metsala J, Lundqvist A, Kaila M, Gissler M, Klaukka T, Virtanen SM. Maternal and perinatal characteristics and the risk of cow's milk allergy in infants up to 2 years of age: a case-control study nested in the Finnish population. *Am J Epidemiol*. 2010;171(12):1310-1316.
26. Metsälä J, Hakola L, Lundqvist A, Virta LJ, Gissler M, Virtanen SM. Perinatal factors and the risk of type 1 diabetes in childhood and adolescence—a register-based case-cohort study in Finland, years 1987 to 2009. *Pediatr Diabetes*. 2020;21:586-596.
27. Zeitler P, Arslanian S, Fu J, et al. ISPAD clinical practice consensus guidelines 2018: type 2 diabetes mellitus in youth. *Pediatr Diabetes*. 2018;19:28-46.
28. Nadeau KJ, Anderson BJ, Berg EG, et al. Youth-onset type 2 diabetes consensus report: current status, challenges, and priorities. *Diabetes Care*. 2016;39(9):1635-1642.
29. Ferraro V, Zanconato S, Carraro S, Ferraro V, Zanconato S, Carraro S. Timing of food introduction and the risk of food allergy. *Nutrients*. 2019;11(5):1131.
30. Harjutsalo V, Reunanen A, Tuomilehto J. Differential transmission of type 1 diabetes from diabetic fathers and mothers to their offspring. *Diabetes*. 2006;55:1517-1524. https://doi.org/10.2337/db05-1296.
31. Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69(1):62-75.
32. Merras-Salmio L, Pelkonen AS, Kolho K-L, Kuitunen M, Mäkelä MJ. Cow's milk–associated gastrointestinal symptoms evaluated using the double-blind, placebo-controlled food challenge. *J Pediatr Gastroenterol Nutr*. 2013;57(3):281-286.
33. Vandenplas Y. Prevention and management of cow's milk allergy in non-exclusively breastfed infants. *Nutrients*. 2017;9(7):731. https://doi.org/10.3390/nu9070731.
34. Høst A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. *Pediatr Allergy Immunol*. 1994;5(5 Suppl):1-36.
35. Saarinen KM, Juntunen-Backman K, Järvenpää AL, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. *J Allergy Clin Immunol*. 1999;104(2 Pt 1):457-461.
36. Pyrhönen K, Näyhä S, Kaila M, Hiltunen L, Läärä E. Occurrence of parent-reported food hypersensitivities and food allergies among children aged 1-4 yr. *Pediatr Allergy Immunol*. 2009;20(4):328-338.
37. Virta LJ, Kautiainen H, Kolho K-L. Symptoms suggestive of cow's milk allergy in infancy and pediatric inflammatory bowel disease. *Pediatr Allergy Immunol*. 2016;27(4):361-367.
38. Fsadni P, Fsadni C, Fava S, Montefort S. Correlation of worldwide incidence of type 1 diabetes (DiaMond) with prevalence of asthma and atopic eczema (ISAAC). *Clin Respir J*. 2012;6(1):18-25.
39. Decreased prevalence of atopic diseases in children with diabetes. *J Pediatr*. 2000;137(4):470-474.
40. Stene LC, Joner G, Norwegian Childhood Diabetes Study Group. Atopic disorders and risk of childhood-onset type 1 diabetes in individuals. *Clin Exp Allergy*. 2004;34(2):201-206.
41. Gazit V, Tasher D, Hanukoglu A, et al. Atopy in children and adolescents with insulin-dependent diabetes mellitus. *Isr Med Assoc J*. 2008;10(12):858-861.
42. Meerwaldt R, Odink RJ, Landaeta R, et al. A lower prevalence of atopy symptoms in children with type 1 diabetes mellitus. *Clin Exp Allergy*. 2002;32(2):254-255.
43. Annunziato F, Romagnani S. Heterogeneity of human effector CD4+ T cells. *Arthritis Res Ther*. 2009;11(6):257.
44. Tuokkola J, Kaila M, Kronberg-Kippilä C, et al. Cow's milk allergy in children: adherence to a therapeutic elimination diet and reintroduction of milk into the diet. *Eur J Clin Nutr*. 2010;64(10):1080-1085.
45. Okada H, Kuhn C, Feillet H, Bach J-F. The "hygiene hypothesis" for autoimmune and allergic diseases: an update. *Clin Exp Immunol*. 2010;160(1):1-9.
46. Matamoros S, Gras-Leguen C, Le Vacon F, Potel G, De La Cochetiere MF. Development of intestinal microbiota in infants and its impact on health. *Trends Microbiol*. 2013;21(4):167-173.
47. Knip M, Siljander H. The role of the intestinal microbiota in type 1 diabetes mellitus. *Nat Rev Endocrinol*. 2016;12(3):154-167.
48. Huang YJ, Marsland BJ, Bunyavanich S, et al. The microbiome in allergic disease: current understanding and future opportunities—2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European academy of allergy and clinical immunology. *J Allergy Clin Immunol*. 2017;139(4):1099-1110.
49. Thompson-Chagoyan OC, Vieites JM, Maldonado J, Edwards C, Gil A. Changes in faecal microbiota of infants with cow's milk protein allergy - a Spanish prospective case-control 6-month follow-up study. *Pediatr Allergy Immunol*. 2010;21(2 PART 2):e394.
50. Rabin RL, Levinson AI. The nexus between atopic disease and autoimmunity: a review of the epidemiological and mechanistic literature. *Clin Exp Immunol*. 2008;153(1):19-30.

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