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Finnish Pediat Diabet Register

2022-05

ORIGINAL ARTICLE

ACTA PÆDIATRICA
NURTURING THE CHILD WILEY

Seasonality in the manifestation of type 1 diabetes varies according to age at diagnosis in Finnish children

Maaret Turtinen[1,2] | Taina Härkönen[1,2] | Jorma Ilonen[3] | Anna Parkkola[1,2] | Mikael Knip[1,2,4] | the Finnish Pediatric Diabetes Register

[1]Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[2]Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland

[3]Immunogenetics Laboratory, Institute of Biomedicine, University of Turku, Turku, Finland

[4]Tampere Center for Child Health Research, Tampere University Hospital, Tampere, Finland

Correspondence
Mikael Knip, Children's Hospital, University of Helsinki, P.O. Box 22 (Stenbäckinkatu 11), FI-00014 Helsinki, Finland.
Email: mikael.knip@helsinki.fi

Funding information
Helsingin ja Uudenmaan Sairaanhoitopiiri; Finska Läkaresällskapet; Medicinska Understödsföreningen Liv och Hälsa; Academy of Finland, Grant/Award Number: 250114 and 292538; Sigrid Juséliuksen Säätiö

Abstract

Aim: We tested the hypothesis of a more aggressive disease process at diagnosis of type 1 diabetes during fall and winter, the colder seasons with consistently observed higher incidence of type 1 diabetes.

Methods: Seasonality in the manifestation of type 1 diabetes was examined in 4993 Finnish children and adolescents. Metabolic characteristics, beta-cell autoantibodies and HLA class II genetics were analysed at clinical diagnosis.

Results: Significant seasonality was observed with higher number of new cases during fall and winter ($n = 1353/27.1\%$ and $n = 1286/25.8\%$) compared with spring and summer ($n = 1135/22.7\%$ and $n = 219/24.4\%$) ($p < 0.001$). The youngest children (aged 0.5–4 years) differed from the older ones (aged 5–14 years) as a minority of them were diagnosed in winter ($p = 0.019$) while the older children followed the same pattern as that seen in the total series. Poorer metabolic decompensation was observed during seasons with lower number of new diagnoses.

Conclusion: The heterogeneity in the seasonality of diabetes manifestation between younger and older children suggests that different environmental factors may trigger the disease at different ages. Poorer clinical condition associated with seasons with a lower number of new cases may be more likely to be due to a delay in seeking medical help than to a more aggressive autoimmunity.

KEYWORDS
autoantibodies, clinical characteristics, HLA class II, season, type 1 diabetes

1 | INTRODUCTION

Seasonal variation in the incidence of type 1 diabetes has been reported with a peak in the fall and winter months.[1-5] The phenomenon seems to be more pronounced in high-incidence countries.[4,6]

Some studies suggest seasonality to be more prominent in males and absent in the youngest children[2,4,7] while others disagree.[1,3,8] However, studies discussing the association of seasonality and the clinical characteristics of type 1 diabetes at diagnosis are sparse.

We set out to delineate the seasonal variation in the manifestation of type 1 diabetes in Finnish children and the association of seasonal timing of diagnosis with clinical presentation, markers of beta-cell autoimmunity and HLA genetics. We also wished to analyse whether seasonal variation is dependent on sex or age. We hypothesised that the clinical presentation is more aggressive in the cold months given the higher number of new cases in that period.

2 | PATIENTS AND METHODS

2.1 | Study design and subjects

Between January 2003 and December 2016, 6913 children and adolescents diagnosed with type 1 diabetes under the age of 15 years were registered in the Finnish Pediatric Diabetes Register (FPDR). We excluded 1747 children because of a lack of blood samples available for the analyses of diabetes-associated autoantibodies and HLA genotyping. The seasonal timing of the type 1 diabetes manifestation was similar between the included and excluded subjects (Table 1). Only the first diagnosed child per family who fulfilled the inclusion criteria was included as an index child. In total, we ended up with 4993 patients, aged between 6 months and 15 years (56.6% male, median age 8.2).

The study subjects were divided into four groups by season of disease presentation. Seasons were classified according to the calendar months: spring (March–May), summer (June–August), fall (September–November) and winter (December–February).

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa. A legal caretaker gave written informed consent and participants 10–15 years of age an informed assent.

2.2 | Metabolic factors

Markers of metabolic decompensation at diagnosis were analysed in the local laboratories, and these included blood pH and the levels of plasma glucose, beta-hydroxybutyrate and HbA1c (available from 2012 onwards). Ketoacidosis was defined as a blood pH <7.30 and severe ketoacidosis as blood pH <7.10. Weight loss, level of consciousness and the puberty status at clinical diagnosis were assessed in the paediatric units and the duration of symptoms before diagnosis by interviewing the parents.

2.3 | Autoantibodies

Insulin autoantibodies (IAA),[9] antibodies to glutamic acid decarboxylase (GADA),[10] islet antigen 2 (IA-2A)[11] and zinc transporter 8 (ZnT8A)[12] were analysed using specific radiobinding assays, and islet cell antibodies (ICA) with indirect immunofluorescence.[13]

Key notes
- Seasonal patterns are seen in the presentation of type 1 diabetes with the highest rate found in fall and winter.
- There is heterogeneity in the seasonality of the disease manifestation between younger and older children suggesting different environmental factors contributing to the disease onset at different ages.
- Poorer metabolic decompensation was observed during the seasons with fewer diagnoses but a clear link between seasonality, metabolic changes and immunology seems to be absent.

The cut-off limits for IAA, GADA, IA-2A and ZnT8A positivity were 2.80 relative units (RU), 5.36 RU, 0.77 RU and 0.50 RU, respectively, based on the 99th percentiles in more than 350 Finnish nondiabetic children and adolescents. According to the Diabetes Autoantibody Standardization Programs and the Islet Autoantibody Standardization Programs between 2003 and 2016, the disease sensitivities and specificities of these assays were 42–62% and 92–99% for IAA, 64–90% and 90–98% for GADA, 62–72% and 93–100% for IA–2A and 48–70% and 97–100% for ZnT8A.

We excluded samples taken later than 30 days after diagnosis (255/4993, 5.1%) since after that the IAA assay may also detect antibodies to exogenous insulin. For calculation of the median antibody titres, only samples at or above the cut-off limit were included in the analyses.

2.4 | HLA genetics

PCR-based amplification followed by hybridisation with lanthanide-labelled probes and time-resolved fluorometry detection was used for HLA typing of the major DR-DQ haplotypes.[14] The HLA susceptibility to type 1 diabetes for each study subject was estimated based on comparison of genotype frequencies between almost 3000 children with type 1 diabetes and their affected family-based artificial controls formed from haplotypes not transmitted to the diabetic child. The susceptibility was classified into six risk groups from strongly decreased risk (risk group 0) to high risk (risk group 5). The DQA1*05-DQB1*02 haplotype was shortened as DR3-DQ2 and the HLA-DRB1*04:01/2/4/5-DQB1*03:02 haplotype as DR4-DQ8.

2.5 | Statistics

We used IBM SPSS Statistics 24 (IBM Corp., Armonk, NY, USA) and the R Software for Statistical Computing for Windows, version 3.5.0 (R foundation, Vienna, Austria, https://cran.r-project.org/)

TABLE 1 Comparison of age at diagnosis, sex and season of type 1 diabetes diagnosis in the study population and excluded subjects (n = 6740)

Demographics	Study subjects n = 4993 (74.1%)	Excluded subjects n = 1747 (25.9%)	p value	Adjusted p value[a]
Age at diagnosis, years, mean (SD)	8.03 (3.89)	7.66 (3.98)	0.001	
Sex, male, % (95% CI)	56.6 (55.2–57.9)	54.7 (52.4–57.1)	0.192	
Season of diagnosis, %			0.512	0.493
Spring	22.7	23.4		
Summer	24.4	24.3		
Fall	27.1	25.4		
Winter	25.8	26.9		

[a]Adjusted for sex and age at diagnosis.

for statistical analyses. We compared the observed frequencies of seasons/months to the expected frequencies of the same variables considering the number of days in each season/month to account for the unequal lengths of months. A mean number of 365.25 days per year and 28.25 days in February was assumed in order to rule in the leap years. Cross-tabulation and Pearson's χ^2 test with continuity correction when appropriate or the Fisher exact test was used for frequencies of categorical variables. Bonferroni's correction for multiple comparisons was not applied due to its overly conservative nature. Differences in levels of parametric variables were analysed with Student's t test or one-way ANOVA and Mann–Whitney U test or Kruskal–Wallis test for nonparametric variables. Adjustment for age at diagnosis and sex was performed with logistic/ordinal/multinomial regression for dichotomous/ordinal/categorical variables and quantile regression in R (package quantreg) for nonparametric variables. A two-tailed p value <0.05 was considered statistically significant.

3 | RESULTS

A majority of the children were diagnosed in fall or winter (n = 1353/27.1% and n = 1286/25.8%) vs. in spring or summer (n = 1135/22.7% and n = 1219/24.4%) ($p = 0.001$). Spring was the season with the lowest number of new cases compared to the other seasons ($p = 0.006$). Analyses by month revealed significant seasonality, with a peak frequency of diagnoses in January followed by August and September, the lowest frequency being observed in May ($p < 0.001$) (Figure 1).

To exclude potential changes in the environment over the years possibly contaminating the results, we looked for the difference in seasonality between those diagnosed in 2009 or earlier and 2010 or later but found no significant differences. The season of birth was not related to the time of disease manifestation.

When examining the whole cohort, there were no differences in the seasonality between sexes. Because of a more apparent seasonality previously observed in older children (aged ≥5 years) than among younger children (aged <5 years),[2,4] we further divided the study population into two groups by age at diagnosis (aged

0.5–4 years and 5–14 years). Within-group analyses were performed by both season and month, and we observed significant seasonality in the subgroup of older children ($p = 0.004$ and $p < 0.001$ respectively) but not in the subgroup of younger children ($p = 0.254$ and $p = 0.395$). Between-group analysis showed a clear difference as a minority of the youngest children were affected in winter while the peak of diagnoses was from fall to winter among the older children (Figure 2). Moreover, this observation was significant in boys but not in girls.

All the analyses were then adjusted for age at diagnosis and sex. Those diagnosed in spring or summer suffered from ketoacidosis more often than those diagnosed in fall (Table 2). Furthermore, weight loss at diagnoses was the highest in summer.

After adjustment, the ICA titres were slightly higher if type 1 diabetes was diagnosed in fall compared with the other seasons (65 Juvenile Diabetes Foundation units [JDFU] vs. 49–64 JDFU, $p = 0.002$). No other differences were found in autoantibody profiles at diagnoses (Table 3). The season was not associated with HLA class II genetics (Table 4).

4 | DISCUSSION

In our nationwide cohort, children were diagnosed with type 1 diabetes more often in the cold seasons, as 52.9% of cases were diagnosed in fall or winter. The frequency is in line with a report from Sweden (53%)[5] while in general, comparisons with previous studies may be challenging because of differences in the research designs and methods used. We did not observe any difference in the seasonality of diabetes manifestation between the sexes. There is a male-to-female excess in patients with type 1 diabetes,[15] and the reason for a more pronounced seasonality in males observed in some reports might reflect a stronger statistical power.

We observed significant seasonality in the group of older children (aged 5–14 years) but not in the group of younger children (aged 0–4 years). A previous report by Weets et al. agree with that finding, although they compared children aged <10 and ≥10 years.[7] Between-group analysis showed a clear difference
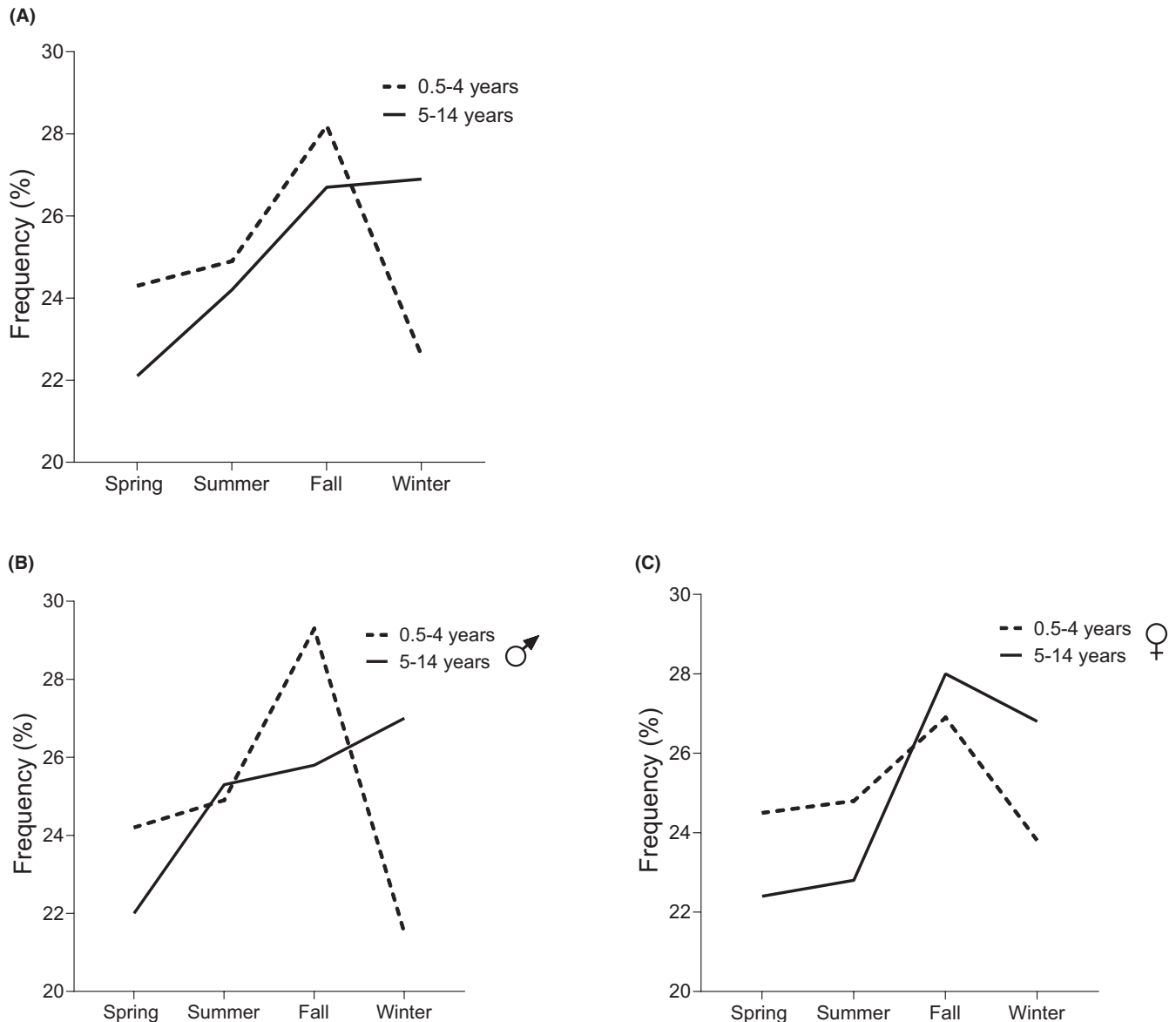
(A)

(B)
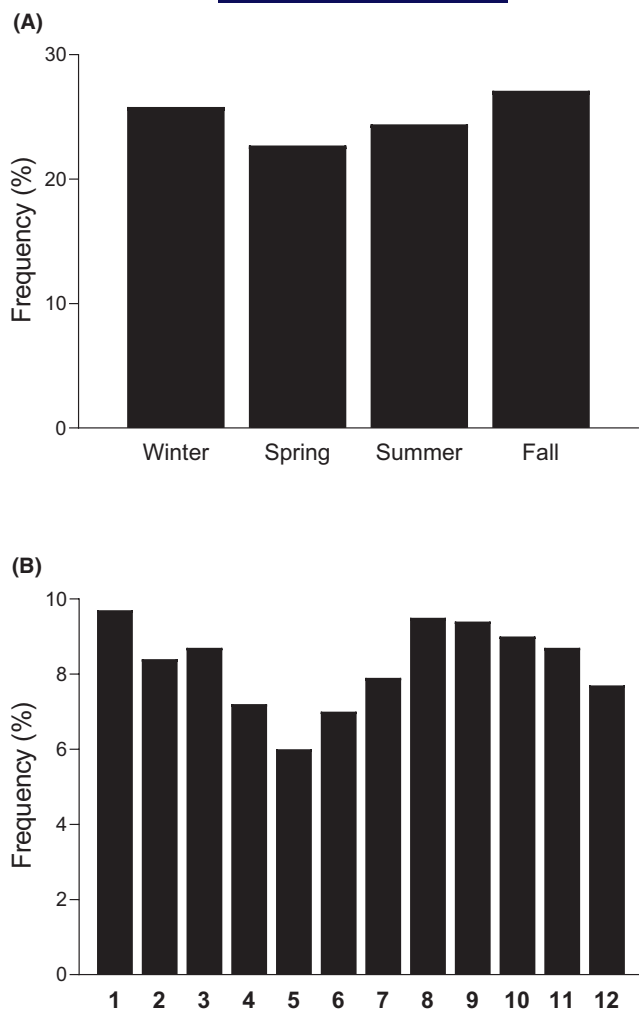
FIGURE 1 Frequencies of type 1 diabetes diagnoses according to season (A) and month (B) presented using histograms. Significant seasonality was observed both in the analyses by season ($p = 0.006$) and by month ($p < 0.001$). Significance was evaluated using the χ^2 test in R after considering the different lengths of seasons/months by comparing the observed frequencies of seasons/months to the expected frequencies of the same variables

D concentrations were associated with islet autoimmunity and multipositivity for diabetes-related autoantibodies, especially in carriers of certain genotypes of the vitamin D receptor gene.[20] Compared with the older children, the vitamin D intake in the younger children might be more closely controlled by the parents, as the families also contact the professionals in the child health clinic more frequently during early childhood. However, based on the results from other large prospective studies, no clear causal link can be confirmed between vitamin D intake or 25(OH)D concentrations and type 1 diabetes.[21,22] The recent observations about the decreasing trend in the incidence rate of the disease only among youngest children[23,24] support the theory of two different endotypes of type 1 diabetes in younger and older children. Our results together with these observations suggest that environmental factors triggering type 1 diabetes in early life may have changed over time and differ from the factors that contribute to the disease progression in older children.

Most studies considering type 1 diabetes seasonality are focused on incidence trends by season whereas we wanted to evaluate the association of seasonality and the disease characteristics at diagnosis. Contrary to our hypothesis, we observed higher frequency of ketoacidosis in spring and in summer and weight loss at diagnosis was the highest if diagnosed in summer. Hanberger et al. reported similar findings of HbA1c as the levels peaked in late spring and summer when the number of children diagnosed with type 1 diabetes was the lowest.[5] The results might be due to the higher risk of dehydration or the masking of increased thirst during the seasons with higher temperature leading to more severe metabolic decompensation, or due to the delay of diagnosis during summer holidays and poorer availability of health services. Similarly, the COVID-19 pandemic has reduced access to medical services resulting in an increased frequency of diabetic ketoacidosis and need for intensive care in children with newly diagnosed type 1 diabetes,[25,26] although underlying causes may be multifactorial.

Interestingly, a few studies have reported a positive correlation between high-incidence seasons and C-peptide levels at diagnosis, suggesting variation in the secretory capability of remaining beta cells by season.[27,28] As classical symptoms and weight loss present less often in children with higher C-peptide concentrations at diagnosis,[28] possibly this could explain our observation of a less severe clinical condition in fall and winter. Unfortunately, we were unable to test this hypothesis, as the FPDR does not provide information on the C-peptide concentrations at diagnosis. Nevertheless, the above-mentioned observations might let us to expect that there should be milder signs of autoimmunity during the high-incidence seasons reflecting heterogeneity on the pathogenic process according to the season of diagnosis. However, we failed to show seasonality in the number of positive autoantibodies at diagnosis and the only notable relationship between season of disease presentation and autoantibodies was higher ICA titres observed in fall. In a small Slovakian study, IA-2A positivity at diagnosis showed seasonal cycling with a peak in fall.[29] Similar seasonality has not been observed in IAA[29] or

as the youngest children had a peak of disease presentation in fall and a nadir in winter in contrast to the older children with peaks both in fall and in winter. Early life infections may contribute to the disease pathogenesis.[16] In particular, a link between certain enteroviruses and progression to clinical type 1 diabetes has been implicated (reviewed in[17]). There is evidence that enteroviruses may function as a trigger of beta-cell autoimmunity but may also be the last inducer of clinical type 1 diabetes. Enteroviruses more often affect younger children, and in Finland, more than 80% of enterovirus infections are diagnosed between August and December.[18] This may explain the peak of type 1 diabetes during fall and the low frequency of disease presentation in winter among the younger children. Some seasonal cycling exists also in the serum 25(OH)D concentrations, as in Finnish children, they are observed to be decreased in winter in parallel with the decreased amount of sunlight.[19] Moreover, decreased 25(OH)

(A)

(B)

(C)

FIGURE 2 Seasonal variation in diabetes onset among children aged 0.5–4 and 5–14 years. The between-group analysis showed a significant difference in the distribution of diagnosis frequencies by season. There was a peak in the frequency of diagnoses during fall and a drop-down during winter among the younger children while the older children were most often diagnosed in fall followed by winter ($p = 0.019$) (A). The phenomenon was more pronounced in the subgroup of boys ($p = 0.020$) (B) and not seen in the subgroup of girls ($p = 0.347$) (C). Significance was evaluated using cross-tabulation and the χ^2 test

GADA at diagnosis.[29,30] Thus, results concerning seasonality in the autoantibody profile at diagnosis are sparse and inconsistent. In a Belgian cohort, seasonality in the diagnosis of type 1 diabetes was restricted to HLA DR3/DR4-negative males.[7] However, we did not find any differences in the HLA genetics between the seasons.

nature of this study is a limitation. There is a possibility of selection bias as 1747 children were excluded because of the lack of samples for analyses. However, the frequencies of seasons of disease presentation did not differ between the included and the excluded children.

4.1 | Strengths and limitations

A strength of this cross-sectional observational study is the large sample derived from a nationwide register including more than 90% of all children diagnosed with diabetes. The retrospective

5 | CONCLUSION

In conclusion, our results from the country with the highest incidence of type 1 diabetes confirmed the seasonality of type 1 diabetes manifestation with peaks in fall and winter. Seasonality

TABLE 2 Seasonal variation in demographic, clinical and metabolic characteristics in type 1 diabetes affected children diagnosed in spring, summer, fall and winter

	n	1. Spring, n = 1135 (22.7%)	2. Summer, n = 1219 (24.4%)	3. Fall, n = 1353 (27.1%)	4. Winter, n = 1286 (25.8%)	p value	Adjusted p value[a]
Demographics							
Sex, male, % (95% CI)	4993	56.0 (53.1–58.9)	58.4 (55.6–61.2)	55.7 (53.0–58.3)	56.2 (53.5–58.9)	0.506	
Age, median (range)	4993	8.04 (0.52–14.98)	7.84 (0.59–14.99)	7.99 (0.82–14.99)	8.49 (0.53–14.98)	0.174	
Familial, % (95% CI)	4993	10.1 (8.4–11.9)	11.2 (9.4–12.9)	9.5 (8.0–11.1)	10.8 (9.1–12.5)	0.541	0.531
Pubertal, % (95% CI)	3764	17.8 (15.3–20.3)	16.4 (14.0–18.7)	17.6 (15.3–20.0)	16.8 (14.4–19.1)	0.819	0.279
Metabolic decompensation at diagnosis							
Duration of symptoms, %	4614					0.067	0.041
No symptoms		1.5	0.5	1.0	0.8		
<1 week		21.0	22.8	23.1	23.2		
1–4 weeks		60.2	55.7	55.8	58.5		
>4 weeks		17.4	20.9	20.2	17.5		1 vs. 2: <0.050
Impaired consciousness, % (95% CI)	4784	5.2 (3.9–6.6)	6.5 (5.1–7.9)	4.9 (3.7–6.1)	5.2 (4.0–6.4)	0.331	0.327
Ketoacidosis, % (95% CI)	4817	18.8 (16.5–21.2)	19.9 (17.6–22.2)	15.8 (13.9–17.8)	17.5 (15.4–19.6)	0.051	0.036
							1 vs. 3: <0.050
							2 vs. 3: <0.050
Severe ketoacidosis, % (95% CI)	4817	3.8 (2.7–5.0)	5.6 (4.3–7.0)	4.4 (3.3–5.5)	4.6 (3.4–5.7)	0.212	0.183
Weight loss, %, median (range)	4610	4.9 (0–33.2)	6.0 (0–32.3)	4.7 (0–40.0)	5.4 (0–28.3)	<0.001	<0.001
							1 vs. 2:0.017
							2 vs. 3: <0.001
							3 vs. 4:0.003
pH, median (range)	4384	7.38 (6.82–7.53)	7.38 (6.82–7.54)	7.38 (6.82–7.53)	7.38 (6.72–7.57)	0.122	0.112
Beta-hydroxybutyrate, mmol/L, median (range)	4384	1.6 (0–18.4)	1.9 (0–17.4)	1.7 (0–27.0)	1.7 (0–23.5)	0.234	0.330
Plasma glucose, mmol/L, median (range)	4869	24.2 (3.2–93.2)	24.5 (3.6–83.2)	23.4 (3.5–97.6)	23.5 (3.6–94.6)	0.079	0.070
HbA1c, mmol/mol, median (range)	841	93.2 (40.0–176.0)	91.0 (38.0–164.0)	90.0 (36.0–189.0)	89.0 (37.7–171.0)	0.700	0.427
HbA1c, %, median (range)	841	10.7 (5.8–18.3)	10.5 (5.6–17.2)	10.4 (5.4–19.4)	10.3 (5.6–17.8)	0.696	0.392

Note: In case of significant differences in the analyses between the four groups of season, paired comparisons by groups were also performed. Only significant p values are presented from the paired analyses.

[a]Adjusted for sex and age at diagnosis.

TABLE 3 Comparison of autoantibody positivity, levels of autoantibodies in positive samples and the number of positive autoantibodies in children diagnosed with type 1 diabetes in spring, summer, fall and winter

Autoantibodies	n	1. Spring, n = 1135 (22.7%)	2. Summer, n = 1219 (24.4%)	3. Fall, n = 1353 (27.1%)	4. Winter, n = 1286 (25.8%)	p value	Adjusted p value[a]
ICA, % (95% CI)	4738	91.7 (90.0–93.3)	92.1 (90.6–93.7)	90.8 (89.2–92.4)	92.4 (90.9–93.9)	0.500	0.434
ICA, JDFU, median (range)	4347	49.0 (3.0–4096.0)	64.0 (3.0–2049.0)	65.0 (3.0–5120.0)	49.0 (3.0–2049.0)	0.335	0.002
							1 vs. 3: 0.007
							2 vs. 3: 0.008
							3 vs. 4: 0.002
IAA, % (95% CI)	4738	42.8 (39.8–45.7)	44.4 (41.6–47.3)	41.8 (39.1–44.5)	43.1 (40.3–45.9)	0.611	0.322
IAA, RU, median (range)	2037	10.7 (2.8–7809.0)	10.3 (2.9–829.8)	10.8 (2.9–343.5)	9.1 (2.8–484.9)	0.123	0.916
IA2A, % (95% CI)	4738	74.8 (72.2–77.4)	75.0 (72.5–77.5)	74.4 (72.0–76.8)	76.0 (73.6–78.4)	0.817	0.847
IA2A, RU, median (range)	3556	102.0 (0.8–453.7)	110.0 (1.0–254.1)	107.2 (0.9–240.9)	104.1 (0.8–553.3)	0.634	0.082
GADA, % (95% CI)	4738	67.6 (64.8–70.4)	66.4 (63.7–69.2)	67.3 (64.7–69.8)	64.2 (61.6–66.9)	0.299	0.248
GADA, RU, median (range)	3144	38.0 (5.5–2675.1)	32.8 (5.4–3051.4)	36.0 (5.4–24849.0)	37.8 (5.5–812.4)	0.570	0.275
Zn8TA, % (95% CI)	4738	68.5 (65.8–71.3)	68.8 (66.3–71.6)	68.6 (66.0–71.1)	71.5 (69.0–74.1)	0.322	0.414
Zn8TA, RU median (range)	3289	13.2 (0.5–209.3)	11.3 (0.5–177.7)	11.8 (0.5–1201.9)	11.9 (0.5–247.5)	0.214	0.798
Number of positive biochemical antibodies, median (mean)	4738	3 (2.54)	3 (2.55)	3 (2.52)	3 (2.55)	0.856	0.980
Number of positive antibodies, median (mean)	4738	4 (3.45)	4 (3.47)	4 (3.43)	4 (3.47)	0.759	0.954
Autoantibody negative, % (95% CI)	4738	2.5 (96.5–98.4)	2.0 (97.2–98.8)	2.2 (97.0–98.6)	2.5 (96.7–98.4)	0.810	0.836
Positivity for multiple (≥2) autoantibodies, % (95% CI)	4738	92.5 (91.0–94.1)	92.8 (91.3–94.2)	91.7 (90.2–93.2)	93.0 (91.6–94.5)	0.599	0.518

Note: In case of significant differences in the analyses between the four groups of season, paired comparisons by groups were also performed. Only significant p values are presented from the paired analyses.

Abbreviations: GADA, antibodies to glutamic acid decarboxylase; IA-2A, antibodies to islet antigen 2; IAA, insulin autoantibodies; ICA, islet cell antibodies; JDFU, Juvenile Diabetes Foundation unit; RU, relative unit; ZnT8A, zinc transporter 8 autoantibodies.

[a]Adjusted for sex and age at diagnosis.

of disease presentation was similar in both sexes. Younger children were most seldom diagnosed in winter whereas the peak of the diagnoses continued from fall to winter in older children, suggesting heterogeneity in environmental factors contributing to type 1 diabetes manifestation in children of different ages. Signs of a poorer metabolic status was observed during the seasons with fewer diagnoses, in spring and summer. However, based on the results from this and previous studies, no clear link can be discerned between seasonality, metabolic decompensation and beta-cell autoimmunity at diagnosis.

TABLE 4 Frequencies of HLA risk genotypes and haplotypes in children diagnosed in spring, summer, autumn and winter ($n = 4993$)

Genetics, % (95% CI)	1. Spring, $n = 1135$ (22.7%)	2. Summer, $n = 1219$ (24.4%)	3. Autumn, $n = 1353$ (27.1%)	4. Winter, $n = 1286$ (25.8%)	p value	Adjusted p value[a]
DR3-DQ2/ DR4-DQ8	20.9 (18.5–23.2)	21.2 (19.0–23.5)	21.1 (19.0–23.3)	22.0 (19.7–24.3)	0.914	0.869
DR3-DQ2/x[b]	16.4 (14.2–18.5)	15.5 (13.5–17.5)	15.7 (13.7–17.6)	13.8 (12.0–15.7)	0.344	0.336
DR4-DQ8/y[c]	47.9 (45.0–50.8)	48.5 (45.7–51.3)	47.7 (45.0–50.3)	47.7 (45.0–50.5)	0.977	0.971
x[b]/y[c]	14.8 (12.7–16.9)	14.8 (12.8–16.8)	15.5 (13.6–17.5)	16.4 (14.4–18.4)	0.636	0.676
DR3-DQ2	37.3 (34.5–40.1)	36.8 (34.0–39.5)	36.8 (34.2–39.4)	35.8 (33.2–38.5)	0.905	0.930
DR4-DQ8	68.8 (66.1–71.5)	69.7 (67.2–72.3)	68.8 (66.3–71.3)	69.7 (67.2–72.2)	0.926	0.905
DR3-DQ2 homozygote	2.3 (1.4–3.2)	2.5 (1.6–3.3)	3.5 (2.6–4.5)	3.6 (2.6–4.6)	0.110	0.112
DR4-DQ8 homozygote	8.6 (7.0–10.3)	7.3 (5.8–8.8)	8.0 (6.5–9.4)	8.6 (7.1–10.2)	0.577	0.627
Risk group					0.080	0.065
0	0.7	0.7	1.0	0.9		
1	1.6	2.7	1.1	2.8		
2	15.6	15.0	16.6	16.3		
3	24.9	22.1	23.7	20.3		
4	36.1	38.2	36.5	37.6		
5	21.1	21.2	21.1	22.1		

Note: In case of significant differences in the analyses between the four groups of season, paired comparisons by groups were also performed. Only significant p values are presented from the paired analyses.

[a]Adjusted for sex and age at diagnosis.

[b]x ≠ DR4-DQ8.

[c]y ≠ DR3-DQ2.

CONFLICT OF INTEREST

The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

ORCID

Mikael Knip https://orcid.org/0000-0003-0474-0033

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