

Original Article

Prevalence of allergic symptoms among children with diabetes mellitus type 1 of different socioeconomic status

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Abstract: The aim of the study was to assess the possible associations between allergies and type 1 diabetes mellitus (DM1), stratified by social class. We studied 127 children with DM1 with a median age of 10.8 yr and 150 controls of comparable age and sex distribution. The parents completed questionnaires on their education and occupation and on their children's history of allergic symptoms, breast-feeding, viral infections, and measles–mumps–rubella (MMR) vaccination. Lower family's social class was more frequently encountered among the DM1 families than in the controls (OR = 0.56, 95% CI: 0.35–0.92). The occurrence of any allergic symptoms among children with DM1 (35.45%) was not significantly different from the controls (38.78%), neither in the total group (OR = 0.87, 95% CI: 0.52–1.45) nor in the stratified analysis by social class. Similar findings were observed regarding the different types of allergic symptoms. In the univariate analysis, breast-feeding, the experience of viral infections, and MMR vaccination were found to be protective of DM1 presentation in both upper and lower social classes. In the multiple logistic regression analysis, the experience of more than 2 infections/yr (OR = 0.12, 95% CI: 0.04–0.34), the origin from middle and upper social classes (OR = 0.42, 95% CI: 0.22–0.80) and breast-feeding (OR = 0.58, 95% CI: 0.31–1.07) were protective of DM1 occurrence. In children with DM1, the presence of allergic symptoms was not associated with the development of DM1. Among the environmental factors, the origin from middle or upper social classes, breast-feeding, the experience of viral infections, and MMR vaccination were found to have a protective effect on DM1 presentation.

**Kyriaki Karavanaki^a,
Eleni Tsoka^b,
Christina Karayianni^a,
Vassilis Petrou^c,
Eleni Pippidou^b,
Maria Brisimitzi^b,
Maria Mavrikiou^b,
Kostas Kakleas^a,
Ilias Konstantopoulos^a,
Manolis Manoussakis^d and
Catherine Dacou-Voutetakis^c**

^aDiabetic Clinic, ^bPediatric Department, University of Athens, Athens, Greece; ^bSecond Pediatric Department 'Aghia Sophia' Children's Hospital, Athens, Greece; ^cEndocrine Unit, ^aPediatric Department, University of Athens, Athens, Greece; and ^dAllergic Department, 'P&A Kyriakou' Children's Hospital, Athens, Greece

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Corresponding author:
Kyriaki Karavanaki, PhD
22 E.Stratou
Filothoi 15237
Athens
Greece.
Tel: 0030-210-6850866;
fax: 0030-210-7774383;
e-mail: kakarav2@yahoo.gr

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Type 1 diabetes mellitus (DM1) is caused by an autoimmune destruction of pancreatic b-cells in genetically susceptible individuals. The autoimmune process is considered to be triggered by certain environmental factors (1–4). An imbalance between T helper (Th)1 and Th2 subfractions of helper T cells toward predominantly Th1 immune reactivity pattern seems to play an important role in the pathogenesis of DM1

(4, 5). In contrast, atopic/allergic conditions are characterized by a predominantly Th2 type immune response (5). It has been previously suggested that there is antagonism between Th1 and Th2 immune responses and that DM1 and atopic diseases may be mutually exclusive on the individual level. It is thus possible that children with DM1 are less prone to develop asthma and other atopic diseases and vice versa (5).

A limited number of epidemiological studies have investigated the association between DM1 and atopic/allergic diseases, which are the most frequent chronic diseases in childhood. In some of these studies, a negative association (6–11) between DM1 and atopic/allergic diseases was detected, while others suggested a positive association (12–14). The inconsistent findings of the above studies could be the result of population differences or differences among various associated environmental factors, such as climatic conditions or dietary habits, in the different countries. No previous study has examined the social class effect on the frequency of allergic symptoms among children with DM1, although either one of these immune-mediated diseases (atopic/allergic diseases and DM1) have been related to the patients' socioeconomic status (15).

Studies published during the past two decades on the effect of socioeconomic status on DM1 presentation showed conflicting results. The majority of these studies demonstrated a higher risk for DM1 in the most wealthy social groups (16, 17), while others (18, 19) suggested that DM1 was more common in families who are socially deprived. Nevertheless, some studies found no association between social class and DM1 (20, 21).

The aims of the present study were: (i) to assess the association of allergic symptoms with the development of DM1 according to socioeconomic status, (ii) to investigate the role of different environmental factors on DM1 occurrence, such as breast-feeding, infections, and vaccination, in a group of patients with diabetes and in controls, also stratified by social class.

Patients and methods

The study population included all newly diagnosed children with DM1 (within 1 month after diagnosis), aged 2.46–15.62 yr, who were diagnosed in two Pediatric Hospitals in Athens within a period of 2 yr (1999–2000). The control population included children, admitted to the Hospital for a temporary problem (hernia, acute appendicitis, and gastroenteritis), who did not have a chronic disease. The control data were collected almost in parallel with the data on children with DM1 and lasted for 3 yr (1999–2001).

The parents of the diabetic and the control children were asked to answer a specific questionnaire, which requested information concerning:

- (i) socioeconomic and family characteristics (parental age, education, and occupation status, marital status, number of siblings);
- (ii) family history of diabetes, allergies, and autoimmune diseases;
- (iii) personal history of children:

- (a) History of allergic symptoms. The allergic symptoms recorded were related to the following diseases: (i) asthma, (ii) atopic dermatitis, (iii) rhinitis, conjunctivitis, (iv) urticaria, angioneurotic edema, (v) food allergy, and (vi) drug allergy. The time period that the allergic symptoms occurred was before DM1 diagnosis and the age of their first occurrence was also recorded.
- (b) Frequency of common viral infections such as 'common viral infections' was considered the viral infections of the upper respiratory tract or the intestine (22). Viruses most likely to cause common viral infections are rhinoviruses, influenza virus, para influenza virus, and rotavirus – diseases for which children are not immunized routinely (22). The frequency of infections was grouped as follows: (i) <2 per yr and (ii) more than 2 infections/yr and refers to the whole time period from birth to the onset of diabetes.
- (c) Time of presentation of common viral infections: (i) during the first 2 yr of life and (ii) later on, until the development of DM1.
- (d) Age and type of immunization with live attenuated viruses [measles–mumps–rubella vaccine (MMR)].
- (e) History of total breast-feeding. The presence of breast-feeding was recorded as a binary variable (yes/no), while its duration was recorded in months.

Occupational social class is usually divided into six groups: professional occupations (I), managerial and technical occupations (II), skilled occupations (III), semi-skilled manual occupations (IV), and unskilled manual occupations (V) (23). In our study, occupational social classes III–V were combined into one category, while classes I and II were separately considered. The estimation of parental social class was based on the educational and occupational status of the two parents simultaneously. More specifically, if both parents were technical school or university graduates and belonged to occupational class I or II, then social class was defined as 'upper'. In cases where both parents were elementary or secondary or, at the most, high school graduates and belonged to occupational classes III, IV or V, then social class was defined as 'lower'. 'Middle' social class included all other cases (i.e. when both parents were unemployed technical school graduates or the father was a university graduate, while the mother had a high school education, etc). Because of the infrequency of such combinations, middle and upper social classes were merged for the purposes of the analysis.

Statistical analysis

Statistical analysis was performed in the statistical package STATA8. Sample characteristics were compared between cases and controls via chi-squared tests, except from the participants' age for which the non-parametric Mann–Whitney test was employed. Univariate analysis included the estimation of exposure-specific DM1 OR using simple logistic regressions. At a second stage, the same relations were assessed separately for the middle/upper and lower social classes. Multiple logistic regression was also employed to assess the potential confounding effect of the recorded factors on the relationship of allergic symptoms with DM1 presentation and to explore whether this relationship was modified by the social classification. As candidate variables for entering in the multiple logistic regression, model were considered covariates with $p < 0.20$ in the corresponding univariate analysis. Binary and multilevel variables were expressed in terms of absolute and relative frequencies, while for continuous variables the medians and interquartile ranges were given. The 5% level was used as the significance level for all tests.

Results

Sample characteristics

Age and sex distribution. The study included 127 children with DM1 (56.35% males and 43.65% females) with recently diagnosed DM1 (within 1 month of diagnosis) and 150 non-diabetic controls (55.33% males and 44.67% females), with comparable sex distribution ($p = 0.866$). The age at diagnosis of the diabetic children ranged from 2.46 to 15.62 yr (median = 10.80), while the age at examination of the controls ranged from 1.24 to 14.50 (median = 10.41; $p = 0.1013$).

Univariate analysis

Parental education, occupation and social class. In terms of paternal education and occupation, no significant difference was observed between the children with diabetes and the controls (Table 1). However, the fathers of the children with DM1 mostly belonged to the lower social classes (50.39%) in comparison with those of the controls (38.36%; $p = 0.046$). Moreover, the mothers of children with diabetes had lower education, that is, elementary and secondary (Table 1) and were more frequently housewives (74.31%) in comparison with those of the controls (57.53%; $p = 0.016$). Thus, children of lower social class was more frequently encountered by diabetes (90.83%) compared with those of the controls (75.34%; $p = 0.001$).

The family's social class definition was based on both paternal and maternal social class. Comparing the family's middle and upper social classes with the lower

class, a significant association of social class with DM1 was observed; the frequency of lower social class was higher among children with diabetes (48.82%) compared with controls (34.93%; $p = 0.020$).

The group of children with DM1 was compared with the control group with respect to the history of allergic symptoms and also the history of common viral infections, vaccination and breast-feeding before DM1 presentation. The differentiation of the above relations according to the parental social class was also assessed. Results are presented in Tables 2–4 in terms of ORs.

Regarding the history of breast-feeding, a protective effect for children with DM1 was observed in the total group (Table 2; OR = 0.47; $p = 0.003$), in the middle and upper social classes (Table 4; OR = 0.36; $p = 0.004$), but not in the lower social class (Table 3). Moreover, short breast-feeding duration (<3 months) was associated with the risk for DM1 presentation both in the total group (Table 2; OR = 0.43; $p = 0.010$) and also in the middle and upper social classes (Table 4; OR = 0.27; $p = 0.009$).

The presence of infections and DM1 were negatively associated (Table 2; OR = 0.41; $p = 0.001$). The protective role of infections was also noted among children of the lower social class (Table 3; OR = 0.26; $p = 0.003$), but not among those of the middle or upper social classes (Table 4). Bacterial infections, in particular, were not significantly associated with DM1 presentation, neither in the total group of diabetic children (Table 2) nor in the stratified analysis by social class (Tables 3 and 4). However, the protective effect of the presence of viral infections on DM1 presentation remained significant in the total group of diabetic children (Table 2; OR = 0.38; $p = 0.003$) and in the lower social class in particular (Table 3, OR = 0.23; $p = 0.005$), but not in the middle or upper social classes (Table 4). Regarding the life period of first exposure to viral infections, the presence of a higher frequency of infections during the first 2 yr of life (Table 2; OR = 0.35; 95% CI: 0.16–0.73), and marginally later on (Table 2; OR = 0.43, 95% CI: 0.24–0.79), were protective of DM1 presentation. This association remained significant for children of the lower social class (Table 3), but not for those of the middle and upper social classes (Table 4). In terms of the frequency of viral infections, two or more infections per year were related to a decreased risk of DM1 compared with the absence of infections (Table 2; OR = 0.14; 95% CI: 0.06–0.32), while the presence of less than two infections per year had a non-significant effect on DM1. Analysis by social class showed that the association between frequency of infections and DM1 remained generally significant in all social classes (Tables 3 and 4).

MMR vaccination also proved to be a significant protective factor against DM1 presentation, both in the total group (Table 2; OR = 0.05, $p < 0.001$) and in the

Table 1. Univariate analysis: parental education, occupation and social class classification in children with DM1 and controls

	n (cases/controls)	Children with DM1 (%)	Controls (%)	OR (95% CI)	p value
Paternal education					
Elementary school	104/145	34 (32.69)	35 (24.14)	Ref	0.193
Secondary school		21 (20.19)	20 (13.79)	1.08 (0.50–2.34)	
High school		18 (17.31)	36 (24.83)	0.51 (0.25–1.08)	
Technical schools		16 (15.38)	24 (16.55)	0.69 (0.31–1.51)	
University		15 (14.42)	30 (20.69)	0.51 (0.24–1.12)	
Maternal education					
Elementary school	104/145	38 (36.54)	16 (11.03)	Ref	<0.001
Secondary school		20 (19.23)	20 (13.79)	0.42 (0.18–0.99)	
High school		29 (27.88)	64 (44.14)	0.19 (0.09–0.40)	
Technical schools		10 (9.62)	15 (10.34)	0.28 (0.10–0.76)	
University		7 (6.73)	30 (20.69)	0.10 (0.04–0.27)	
Paternal occupation*					
I	127/146	19 (14.96)	24 (16.44)	Ref	0.240
II		44 (34.65)	63 (43.15)	0.88 (0.43–1.80)	
III		64 (50.39)	59 (40.41)	1.37 (0.68–2.75)	
Maternal occupation*					
I	109/146	10 (9.17)	18 (12.33)	Ref	0.016
II		18 (16.51)	44 (30.14)	0.74 (0.29–1.90)	
III		81 (74.31)	84 (57.53)	1.74 (0.76–3.98)	
Paternal social class					
Lower	127/146	64 (50.39)	56 (38.36)	Ref	0.046
Upper		63 (49.61)	90 (61.64)	0.61 (0.38–0.99)	
Maternal social class					
Lower	109/146	99 (90.83)	110 (75.34)	Ref	0.001
Upper		10 (9.17)	36 (24.66)	0.31 (0.15–0.65)	
Family's social classt					
Lower	127/146	62 (48.82)	51 (34.93)	Ref	0.020
Upper		65 (51.18)	95 (65.07)	0.56 (0.35–0.92)	

DM1, type 1 diabetes mellitus; Ref, reference category.

*I, professional occupations; II, managerial and technical occupations; III, skilled (non-manual), semi-skilled manual, unskilled manual occupations, unemployed, students, and housewives.

†Family's social class has been defined with three levels based on the paternal and maternal social classes: lower, middle and upper. Here middle and upper social classes are compared with the lower social classes.

various social classes (Tables 3 and 4). The age of MMR vaccination was significantly higher in the total group of diabetic children in comparison with the controls (Table 2; OR = 1.59, $p = 0.046$), and also in the lower (OR = 4.33, $p = 0.010$) but not in the middle and upper social classes (Tables 3 and 4).

The occurrence of any allergic symptoms was not associated with DM1 presentation neither in the total group (OR = 0.87; $p = 0.586$) (Table 2), nor in the stratified analysis by social class (Tables 3 and 4). In terms of the life period of first manifestation, the occurrence of allergic symptoms was not found to affect DM1 presentation, neither in the total group (Table 2) nor in the stratified analysis by social class (Tables 3 and 4). Moreover, when analyzing the social class stratification of allergic symptoms among the controls, the development of allergic symptoms was more frequent in the middle and upper social classes (42/56, 75%) than in the lower social class (14/56, 25%) ($\chi^2 = 4.020$, $p = 0.045$). Inversely, in the group of children with DM1, no significant social class differentiation in the frequency of allergic symptoms was observed (middle and upper social classes: 19/39, 48.7% vs.

lower social classes: 20/39, 51.28%) ($\chi^2 = 0.040$, $p = 0.842$).

Multivariate analysis

A multiple logistic regression model was used to assess the effect of allergic symptoms on DM1 presentation, adjusting for certain environmental factors. Thus, the frequency of infections, breast-feeding, and social class constitute the final set of covariates (Table 5). Moreover, the life period of first exposure to infections has also been taken into account, without any modification on the above covariates. Although MMR vaccination was significant in the univariate analysis, it could not be included in the multivariate analysis as it would obscure the relationship of the other parameters with DM1 presentation. According to the final model, the experience of two or more infections per year was associated with a decreased risk of DM1 compared with the absence of infections (OR = 0.12, 95% CI: 0.04–0.34). However, multivariate analysis confirmed the significant association between social class and DM1 presentation, indicated primarily in the univariate analysis

Table 2. Univariate analysis: the effect of different environmental factors on diabetes presentation in children with DM1 and controls

	n (cases/ controls)	Children with DM1 (%)	Controls (%)	OR (95% CI)	p value
Breast-feeding					
Breast-feeding	121/150	63 (52.07)	105 (70.00)	0.47 (0.28–0.77)	0.003
Breast-feeding duration (in months)*	121/150	0.5 (0–9)	2 (0–9)	0.93 (0.86–1.01)†	0.076
Breast-feeding duration					
No breast-feeding	121/150	58 (47.93)	45 (30.00)	Ref	0.010
<3 months		25 (20.66)	45 (30.00)	0.43 (0.23–0.81)	
≥3 months		38 (31.40)	60 (40.00)	0.49 (0.28–0.86)	
Infections					
Infections	126/99	61 (48.41)	69 (69.70)	0.41 (0.23–0.71)	0.001
Type of infection					
No infection	126/99	65 (51.59)	30 (30.30)	Ref	0.003
Viral		53 (42.06)	64 (64.65)	0.38 (0.22–0.67)	
Bacterial		8 (6.35)	5 (5.05)	0.74 (0.22–2.45)	
Life period of first exposure to infection(s)					
No infection	125/99	65 (52.00)	30 (30.30)	Ref	0.004
First 2 yr of life		18 (14.40)	24 (24.24)	0.35 (0.16–0.73)	
Later on		42 (33.60)	45 (45.45)	0.43 (0.24–0.79)	
Infections frequency					
No infection	118/96	65 (55.08)	30 (31.25)	Ref	<0.001
<2 times/yr		43 (36.44)	33 (34.38)	0.60 (0.32–1.13)	
≥2 times/yr		10 (8.47)	33 (34.38)	0.14 (0.06–0.32)	
Vaccination					
MMR vaccination	106/97	51 (48.11)	92 (94.85)	0.05 (0.02–0.13)	<0.001
Age at MMR vaccination*	51/92	1.5 (1.0–4.0)	1.3 (1.2–3.9)	1.59 (1.01–2.50)†	0.046
Allergic symptoms					
Allergies	110/147	39 (35.45)	57 (38.78)	0.87 (0.52–1.45)	0.586
Type of allergy					
No allergy	110/147	71 (64.55)	90 (61.22)	Ref	0.692
Asthma		15 (13.64)	23 (15.65)	0.83 (0.40–1.70)	
Atopic dermatitis/rhinitis, conjunctivitis		9 (8.18)	11 (7.48)	1.04 (0.41–2.64)	
Urticaria, angioneurotic edema		11 (10.00)	12 (8.16)	1.16 (0.48–2.79)	
Food or drug allergy		4 (3.64)	11 (7.48)	0.46 (0.14–1.51)	
Life period of first exposure to allergy					
No allergy	82/117	71 (86.59)	90 (76.92)	Ref	0.061
First 2 yr of life		3 (3.66)	15 (12.82)	0.25 (0.07–0.91)	
Later on		8 (9.76)	12 (10.26)	0.85 (0.33–2.18)	

DM1, type 1 diabetes mellitus; Ref, reference category.

*Reported are the median values and the respective interquartile ranges.

†OR for 1 unit increase in the 'exposure'.

(Table 1). More specifically, children of the middle or upper social classes had a lower risk to develop DM1 compared with children of the lower social class (Table 5; OR = 0.42; 95% CI: 0.22–0.80). Finally, given the frequency and age at first presentation of viral infections and a specific social classification, breast-feeding was found to have a marginally significant protective effect on DM1 presentation (Table 5; OR = 0.58; 95% CI: 0.31–1.07).

Discussion

Our findings indicate that the presence of DM1 was not antagonistic toward allergic diseases in the total group of patients with DM1 and also stratified by social class. Moreover, our study confirmed that the origin from middle and upper social classes, breast-feeding, the

experience of viral infections in early childhood, and MMR vaccination have a protective effect on DM1 presentation. There is no previous study, to our knowledge, assessing the effect of social class on the frequency of allergic symptoms among children with DM1.

It is broadly accepted that both DM1 and atopic/allergic conditions present in genetically susceptible individuals; however, certain environmental factors, and among them viral infections, may play a significant role in the earlier onset of symptoms. Previous studies on the role of infections, as factors affecting the development of DM1 have given controversial results. Indeed, the presence of infections during the 6 months before the diagnosis of DM1 (24) or during the fetal life (25) has been considered as a factor precipitating diabetes presentation or triggering diabetes-related autoimmunity, respectively. Inversely, according to

Table 3. Analysis by social class: the effect of different environmental factors on diabetes presentation in children with DM1 and controls of the lower social class

	n (cases/ controls)	Children with DM1 (%)	Controls (%)	OR (95% CI)	p value
Breast-feeding					
Breast-feeding	62/51	31 (50.00)	29 (56.86)	0.76 (0.36–1.60)	0.467
Breast-feeding duration (in months)†	62/51	0.25 (0–9)	1 (0–9)	0.95 (0.84–1.08)*	0.461
Breast-feeding duration					
No breast-feeding	62/51	31 (50.00)	22 (43.14)	Ref	0.739
<3 months		15 (24.19)	13 (25.49)	0.82 (0.33–2.06)	
≥3 months		16 (25.81)	16 (31.37)	0.71 (0.29–1.72)	
Infections					
Infections	62/34	26 (41.94)	25 (73.53)	0.26 (0.10–0.65)	0.003
Type of infection					
No infection	62/34	36 (58.06)	9 (26.47)	Ref	0.005
Viral		21 (33.87)	23 (67.65)	0.23 (0.09–0.58)	
Bacterial		5 (8.06)	2 (5.88)	0.63 (0.10–3.76)	
Life period of first exposure to infection(s)					
No infection	61/34	36 (59.02)	9 (26.47)	Ref	0.007
First 2 yr of life		5 (8.20)	7 (20.59)	0.18 (0.05–0.70)	
Later on		20 (32.79)	18 (52.94)	0.28 (0.11–0.73)	
Infections frequency					
No infection	58/32	36 (62.07)	9 (28.13)	Ref	0.002
<2 times/yr		14 (24.14)	9 (28.13)	0.39 (0.13–1.18)	
≥2 times/yr		8 (13.79)	14 (43.75)	0.14 (0.05–0.44)	
Vaccination					
MMR vaccination	49/33	19 (38.78)	31 (93.94)	0.04 (0.01–0.19)	<0.001
Age at MMR vaccination†	19/31	1.5 (1.2–2.0)	1.3 (1.3–1.5)	4.33 (0.68–27.80)*	0.010
Allergic symptoms					
Allergies	55/50	20 (36.36)	14 (28.00)	1.47 (0.64–3.36)	0.359
Type of allergy					
No allergy	55/50	35 (63.64)	36 (72.00)	Ref	0.530
Asthma		9 (16.36)	5 (10.00)	1.85 (0.56–6.07)	
Atopic dermatitis/rhinitis, conjunctivitis		4 (7.27)	0 (0.00)	—	
Urticaria, angioneurotic edema		6 (10.91)	6 (12.00)	1.03 (0.30–3.50)	
Food or drug allergy		1 (1.82)	3 (6.00)	0.34 (0.03–3.46)	
Life period of first exposure to allergy					
No allergy	42/42	35 (83.33)	36 (85.71)	Ref	0.924
First 2 yr of life		3 (7.14)	3 (7.14)	1.03 (0.19–5.45)	
Later on		4 (9.52)	3 (7.14)	1.37 (0.29–6.58)	

DM1, type 1 diabetes mellitus; Ref, reference category.

*Reported are the median values and the respective interquartile ranges.

†OR for 1 unit increase in the 'exposure'.

the hygiene hypothesis, the lower exposure to infections during the first years of life, which is more frequent in families with decreasing size, and high socioeconomic status (26) might contribute to the rising prevalence of immune-mediated diseases, such as atopic/allergic diseases and autoimmune diseases. Our data support the hygiene hypothesis because the experience of two or more viral infections/year was protective of DM1 development in the total group of patients and also in the different social classes.

The relationship between atopic disease and autoimmunity is controversial. According to the Th1/Th2 imbalance theory (27, 28), individuals may develop a Th1-weighted phenotype, which predisposes them to autoimmunity or a Th2-weighted phenotype, which may predispose them to atopy. The development of these phenotypes seems to be under genetic control and may be affected by environmental factors (29, 30).

Many studies support the protective effect of a Th2-weighted imbalance against autoimmune disorders and suggest that the presence of allergic symptoms may confer partial protection against DM1 (10, 11, 31, 32). However, others challenge the Th1/Th2 imbalance theory and consider it as an oversimplification, based on the temporal parallel increase of both autoimmune and allergic diseases. Thus, Caffarelli et al. (33) reported lower prevalence of allergic symptoms in children with DM1 than in controls, but found no significant difference between the two groups in terms of immunoglobulin E (IgE) sensitization, which is a Th2-mediated process. Kero et al. (34) reported that the incidence of asthma in children with DM1, celiac disease or rheumatoid arthritis was higher than in children without these autoimmune diseases. Moreover, Sheikh and Hubbard (35) found a positive association between atopy and common autoimmune

Table 4. Analysis by social class: the effect of different environmental factors on diabetes presentation in children with DM1 and controls of the middle and upper social classes

	n (cases/ controls)	Children with DM1 (%)	Controls (%)	OR (95% CI)	p value
Breast-feeding					
Breast-feeding	59/95	32 (54.24)	73 (76.84)	0.36 (0.18–0.72)	0.004
Breast-feeding duration (in months)†	59/95	1 (0–9)	2 (0–9)	0.93 (0.84–1.04)*	0.209
Breast-feeding duration					
No breast-feeding	59/95	27 (45.76)	22 (23.16)	Ref	0.009
<3 months		10 (16.95)	30 (31.58)	0.27 (0.11–0.68)	
≥3 months		22 (37.29)	43 (45.26)	0.42 (0.19–0.89)	
Infections					
Infections	64/63	35 (54.69)	43 (48.25)	0.56 (0.27–1.16)	0.116
Type of infection					
No infection	64/63	29 (45.31)	20 (31.75)	Ref	0.280
Viral		32 (50.00)	40 (63.49)	0.55 (0.26–1.15)	
Bacterial		3 (4.69)	3 (4.76)	0.69 (0.13–3.77)	
Life period of first exposure to infection(s)					
No infection	64/63	29 (45.31)	20 (31.75)	Ref	0.290
First 2 yr of life		13 (20.31)	16 (25.40)	0.56 (0.22–1.42)	
Later on		22 (34.38)	27 (42.86)	0.56 (0.25–1.25)	
Infections frequency					
No infection	60/62	29 (48.33)	20 (32.26)	Ref	<0.001
<2 times/yr		29 (48.33)	23 (37.10)	0.87 (0.39–1.92)	
≥2 times/yr		2 (3.33)	19 (30.65)	0.07 (0.02–0.35)	
Vaccination					
MMR vaccination	57/62	32 (56.14)	59 (95.16)	0.07 (0.02–0.23)	<0.001
Age at MMR vaccination†	32/59	1.5 (1–3)	1.4 (1.3–3.9)	1.34 (0.78–2.28)*	0.288
Allergic symptoms					
Allergies	55/93	19 (34.55)	42 (45.16)	0.64 (0.32–1.28)	0.203
Type of allergy					
No allergy	55/93	36 (65.45)	51 (54.84)	Ref	0.563
Asthma		6 (10.91)	17 (18.28)	0.50 (0.18–1.39)	
Atopic dermatitis/rhinitis, conjunctivitis		5 (9.09)	11 (11.83)	0.64 (0.21–2.01)	
Urticaria, angioneurotic edema		5 (9.09)	6 (6.45)	1.18 (0.33–4.17)	
Food or drug allergy		3 (5.45)	8 (8.60)	0.53 (0.13–2.14)	
Life period of first exposure to allergy					
No allergy	40/71	36 (90.00)	51 (71.83)	Ref	0.460
First 2 yr of life		0 (0.00)	11 (15.49)	—	
Later on		4 (10.00)	9 (12.68)	0.63 (0.18–2.20)	

DM1, type 1 diabetes mellitus; Ref, reference category.

*Reported are the median values and the respective interquartile ranges.

†OR for 1 unit increase in the 'exposure'.

disorders. In contrast with the above, Stromberg et al. (26) reported a similar prevalence of atopic disease in total, and also of the different types of allergic symptoms, skin prick test results, total serum IgE levels, and circulating IgE antibodies to allergens between a group of children with DM1 and age- and sex-matched controls. In agreement with the latter study, we found that there was no difference in the frequency of allergic symptoms in total and also of the different types of allergy between children with DM1 and controls. We also found similar findings in the stratified analysis by social class. A possible explanation for the conflicting data on the association between allergy and autoimmunity is that the exposure to infections in early life may either stimulate a shift away from a predominantly Th2 response or may affect the maturation across the immune system with the down-regulation of both Th1 and Th2 responses (35). It has

been recently suggested that these two different effects of infections could be associated with the anti-inflammatory cytokine interleukin (IL)-10 (36), which is secreted by both Th1 and Th2 effector cells (37). Thus, lack of exposure to infections in early childhood could lead to lack of IL-10 and possibly other down-regulating factors, leading to both Th1- and Th2-mediated diseases in later life.

The role of MMR vaccination in relationship with the development of DM1 has been broadly previously discussed with conflicting results. Mumps vaccination has been suggested (38) to induce b-cell autoimmunity. Inversely, a decreased incidence of DM1 has been previously reported following measles (39) or MMR vaccinations (40, 41). The latter (40, 41) studies consider MMR vaccination as a preventive factor of infectious diseases, which is possibly related to DM1 presentation. MMR vaccination in our study was

Table 5. Multivariate analysis: logistic regression results on the covariates that affect DM1 presentation

	OR	95% CI	p value
Age at first presentation of infections			
No infection	Ref		
First 2 yr of life	—	—	—
Later on	0.99	(0.10–2.41)	0.975
Frequency of infections			
No infection	Ref		
<2 times/yr	0.74	(0.29–1.90)	0.532
2 times/yr	0.12	(0.04–0.34)	<0.001
Social class			
Lower	Ref		
Middle and upper	0.42	(0.22–0.80)	0.008
Breast-feeding	0.58	(0.31–1.07)	0.083

DM1, type 1 diabetes mellitus; Ref, reference category.

found to be a significant protective factor against DM1 presentation, both in the total group of patients and also in the various social classes. These data could be interpreted as indicating lower stimulation of the immune system, leading to DM1 susceptibility, in accordance with the hygiene hypothesis (42).

In terms of breast-feeding and its role in the development of DM1, it has been suggested that hygiene and semi-sterile diet might affect the pattern of bacterial colonization of the gastrointestinal tract and could have a preventive effect on inappropriate immune responses to allergens or autoantigens (8). Moreover, the short duration of breast-feeding has been related to the development of diabetes-related autoimmunity (43). According to our univariate analysis, breast-feeding was found to be less frequently encountered and of shorter duration among children with DM1 than among controls and seemed to have a marginally significant protective effect on DM1 presentation.

With regard to the social class differentiation in the presentation of different allergic reactions, asthma has been generally associated with lower social classes (44, 45). Possible confounders in the association of asthma with socially underprivileged could be family size or birth order, increased frequency of infections in early childhood (the hygiene hypothesis) (42, 46) and low maternal education (47), or other factors, that is, air pollution, housing conditions, domestic mold growth, obesity, diet and smoking (46, 48). On the contrary, atopy in general (49) and especially hay fever or eczema have been reported to be more frequent in the upper social classes (15). In agreement with the above studies, in our study in the control group, the total frequency of allergic symptoms was increased in the middle and upper social classes in comparison with the lower class. Nevertheless, in the group of children with DM1, no social class differentiation in the frequency of allergies was observed.

In terms of the relationship of DM1 with different socioeconomic status, previous studies report conflict-

ing results (16–22), which could be attributed to the different measures of socioeconomic status used in various studies. Socioeconomic disadvantage usually has been measured in epidemiological studies by individual indicators (education, occupation, house ownership, quality and amenities, and income) (50) and by area-based indicators (residential areas drawn from census data or aggregate income) (51). In our study, social class was assessed by the combination of occupational and educational status of both parents and, using this definition, children from lower social class had a higher risk for DM1 presentation. It is possible that different factors that may be affected by the parental socioeconomic and educational status, such as diet, lifestyle, and breast-feeding practices (17), could explain the predominance of lower social class among the children with DM1 of our study.

An important methodological problem in a case-control study, including patients with a chronic disease, such as our patients, is the recall bias (52). This is because of the possible differential recall by the parents of DM1 patients of events of the medical history of their children and of those of the healthy controls. As in our study, all children with DM1 were recently diagnosed (within the past month); it is more likely that the information on allergic symptoms are valid. However, a differential recall between the families of children with diabetes and the controls cannot be totally excluded because the active diagnosis of diabetes might affect the reflection of other diseases in the families.

In conclusion, in our study, the presence of allergic symptoms was not affected by DM1 presentation neither in the total group of patients nor in the stratified analysis by social class. Among the environmental factors, the origin from lower social classes and also the reduced frequency of breast-feeding, of viral infections, especially in early childhood and of MMR vaccination were factors precipitating the development of DM1. Thus, it is possible that exclusive and prolonged breast-feeding, attending day/care centers and regular vaccination may protect against autoimmunity. These observations suggest that common environmental factors, resulting in immunologic stimulation at an early age, may prevent the development of both autoimmune diseases and atopic/allergic diseases, which are not mutually exclusive.

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