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Childhood Diabetes type 1 in the Netherlands: Incidence, Clinical Presentation and Initial Treatment during 1996-1999

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Abstract

Objective
Firstly, to determine the incidence of diabetes type 1 in the children from 0 to 14 years in the Netherlands during 1996-1999. The incidence will be compared in advancing age groups (0-4, 5-9 and 10-14) as well as with the results of previous Dutch incidence studies performed during the 1978-1980, 1988-1990 and 1993-1995 years. The characteristics of the child with diabetes are also analyzed: its average age at presentation, gender dependency or preference for ethnicity.

The second objective concerns the clinical presentation of the newly diagnosed child. The reported symptoms judged by the treating pediatricians and the laboratory tests will be compared to the initial treatment given to the new patient: home versus hospital based.

Research Design and Methods
The Dutch Pediatric Surveillance Unit was instrumental in this study with its registration cards and questionnaires, mailed to all practicing pediatricians in the Netherlands. Through the Dutch Diabetes Association, a questionnaire supplied by TNO was sent to its members. This second questionnaire served as an independent source to correct the incompleteness of the DPSU register, attain the ascertainment and consequently estimate the incidence and its 95% confidence interval. The incidence increase rate was calculated by comparison with the first Dutch incidence study of 1978-1980. Also, the ratio of incidence for the youngest age group was determined from 1978 onwards.

In the DPSU questionnaire, the clinical presentation of the newly diagnosed child is characterized by scores the pediatrician gave on the child's conscience and hydration status, as well as by the results of its serum glucose level, blood pH value and the presence of ketonuria. All these items of clinical presentation were compared to the child's initial treatment: home or hospital based. The statistical analysis was performed by chi square analysis using the SPSS 10.0 program.

Results
The incidence of diabetes type 1 in Dutch children aged 0-14 years during 1996-1999 is 18.6/100.000/year (95% CI 17.7 - 19.4). In the ascending age groups, (0-4, 5-9 and 10-14 years old) the incidence is respectively: 12.9/100.000/year (95% CI 12.0 - 13.9), 19.3 (18.0 - 20.7) and 24.2 (21.9 - 26.6). In comparison with the overall incidence established in 1978-1980, the average annual increase rate in the overall group is 3.6% (68% increase over an 18.5 year period). In the different age groups studied, the highest increase rate per annum is measured in the children aged 0-4 years old: 4.8% (90% increase over 18.5 years).

The DPSU received a total of 1,284 questionnaires fit to analyze. The mean age of a newly diagnosed child with diabetes type 1 was 7.6 years (95% CI 7.4 - 7.9) compared to 8.0 (7.8 - 8.3) in 1993-1995, and 9.2 (9.0 - 9.5) in 1988-1990. The male preference in the diabetic children, the male:female ratio is 1.07 (0.97 - 1.21), reflects that in the age matched population (1.05). The ethnicity in the Dutch children with diabetes showed overrepresentation: 4.9% of the newly diagnosed children were Moroccan descent, compared to 1.2% of Turkish descent. It is also noted that children from Somali mothers account for 0.8% of all diabetic children in the Netherlands.

The questionnaires show that, according to the treating pediatricians, over time more children have normal consciousness: in 1993-1994 81.2 %, now 86.5 %. Normal hydration status was judged previously in 56.7 % of the cases, now 63.9 %. The corresponding laboratory values reported show similar improvements. The mean serum glucose level decreased form 31.4 mM to 30.6 mM, the mean blood pH value improved from 7.31 to 7.34, and the presence of ketonuria diminished from 72.9% to 68.3%. This overall improvement did coincide with more children initially being treated at home. Indeed, 15% of the newly diagnosed children stayed at home and had not been admitted into the hospital. In a previous study (1993-1994), this group consisted of 11%. However, the treatment strategy of the Dutch pediatricians showed low and partial association with either age or severity of the clinical characteristics of the newly diagnosed children with diabetes type 1. In all age groups equally, 15% of the children had initially been treated at home. Moreover, 4% of the more seriously afflicted children with signs of ketoacidosis had been successfully managed at home at the moment of diagnosis. Other factors inhibit home treatment.

Discussion

The incidence increase pattern suggests an environmental contribution causing earlier development of diabetes type 1.The mean age at presentation has decreased, suggesting the environmental contribution towards diabetes type 1 to occur during early life. Migration from Somalia and Morocco to the Netherlands is associated with more children with diabetes type 1. This unique phenomenon could reflect environmental differences between the various migrating residents in the Netherlands.

The overall clinical condition of the average newly diagnosed child with diabetes has improved. Awareness in the population and referral to the pediatric practice is more effective: deviations in laboratory results improved. The percentage of children initially treated at home has increased. However, the choice appeared not to be defined solely by age or clinical condition. The choice home or hospital based initial management seems also determined by geographical distribution and the quality or experiences with home care management.

Conclusion and Recommendation

Due, primarily to unidentified environmental factors, diabetes type 1 occurs still earlier in childhood and seriously affects the prospects for public health. We recommend, to explore prevention strategies that combine next to genetically predisposition, the environment from intrauterine life on, in groups of children most seriously afflicted. We also recommend, to increase the ascertainment of the DPSU.

During 1996-1999, children are newly diagnosed with milder symptoms and improving laboratory results. Home care management should therefore be available for all Dutch pediatricians. We recommend, to agree on a feasible standard of outpatient treatment nationwide.

Contents

1 Introduction

Diabetes type 1 is an immune-mediated disorder that leads to the destruction of pancreatic β-cells. When approximately 70% of the initial β-cell mass has been destroyed by a cellular-mediated autoimmune reaction, the disease is clinically manifested. Diabetes type 1 is favored by a genetic predisposition linked to the HLA system, the major gene being located on the HLA locus of chromosome 6. Diabetes type 1 is strongly associated with the class II molecules, which encode for the D allele. People who express the DR3 or DR4 alleles or those who are heterozygous (DR3/DR4) are especially susceptible to develop type 1 diabetes. Great importance has also been attributed to certain DQ haplotypes. The favoring HLA haplo-types permit the action of environmental factors (probably certain viral and chemical agents) with cell membrane components (the HLA molecules) to present antigens to the T lymphocyte, thus triggering the destructive autoimmune reaction. Common viral infections and cytokines (cytomegaly, coxsackie, mononucleosis, hepatitis, enterovirus), common toxins or dietary factors (β-casein in cow's milk e.g.) are linked in this respect to the most common form of type 1 diabetes (Belfiore F and Iannello S, 2000; Hiemstra HS, et al. 2001; Vreugdenhil GR, 2001). Two prevention trials in first-degree relatives of diabetes type 1 affected individuals are presently in progress: the American Diabetes Prevention Trial-1 and the European Nicotinamide Diabetes Intervention Trial (Schatz DA and Bingley PJ, 2001). For the general population, screening for the risk to develop diabetes type 1 is available by HLA typing (Dorman JS and Bunker CH, 2000).

However, the HLA genes involved are 'susceptibility genes' which modify the risk, they may not always be required and are not solely sufficient for diabetes type 1 development. Other not specified environmental factors support diabetes type 1 expression in either a causative or a protective role. From the prospect of prevention in the general population these items are also relevant. Although the genetic influence on the disease is incontrovertible, environmental factors play a crucial role in its development and offer a wealth of theoretical opportunities for prevention (Åkerblom HK and Knip M, 1998: Chowdhury TA, et al. 1999). Environmental factors may have the potency to be avoided or favored. Identified factors relate to life style, growth and general health (Bruining GJ, et al. 2000). Obesity and rapid linear growth in childhood are risk factors for diabetes type 1 (Hyppönen E, et al. 2000). Prevention of infant and childhood obesity may be a major factor in preventing childhood diabetes type 1. Other factors involved are perinatal risk factors like older maternal age, maternal pre-eclampsia, neonatal respiratory disease and jaundice caused by blood group incompatibility (Dahlguist GG, et al. 1999). Others are more difficult to point at: e.g. weak associations like with birth weight need large studies to be identified (Stene LC, et al. 2001). Some attributions are only identified on a worldwide scale, like dietary preferences. The rise in consumption of meat and dairy products are predictors of an elevated incidence rate of diabetes type 1, whereas consuming cereals is an inverse predictor (Muntoni S, et al. 2000). The bioavailability of single nutrients like vitamin D (Cantorna MT, 2000) and Zn (Haglund B, et al. 1996) e.g. are suggested to be relevant in this aspect. Since nutrition has such a central role in the risk for obesity, and nutrition in fetal life seems a central stimulus for programming of susceptibility for disease later in life, timing and balance of nutrients during pregnancy should also be considered in the risk for the development of childhood diabetes type 1 (Harding JE, 2001).

From the perspective of public health and prevention, relevant environmental factors need to be identified, specified and judged on their combined or single power as a tool for intervention studies, besides genetic screening. Avoidance at critical age could prevent diabetes to manifest itself (early) in childhood. Epidemiological studies in different social and ethnic groups may identify successful strategies for prevention to be

implemented. Incidence studies also give some perspective as to how serious this medical condition is. It stresses not only the importance for prevention but a delay to the onset of this disease. Children who develop diabetes at a young age suffer for a long time the repercussions of the illness and will suffer more extensive and severe complications later in life. In adults progressive chronic complications affecting vital organs will entail premature disability and mortality, requiring social and financial expenses that will exceed available sources. In previous epidemiological studies performed in 1978-1980 (Vaandrager GJ, 1984), 1988-1990 (Hirasing RA, 1995) and 1993-1995 (Reeser HM, 1998), it was estimated that the incidence of diabetes did increase in the Netherlands. The study presently under hand, aims to determine how the incidence of diabetes among 0-14 year olds during the period of 1996 to 1999 has increased further, and will focus on the specific aspects of the increase. Minority groups in the Netherlands show different trends. Moroccan children have incidences, three to four times, higher then other minority groups (Vos C, et al. 1997). This trend is being investigated in a related research at the TNO institute (Mokadem N el, et al. 2001).

Awareness of the symptoms and signs of diabetes in the population is needed. The health services are confronted with increasing investment to guarantee sufficient care in the future. Since there are more patients, the question arises as to the care the child will receive. There is an on going discussion as to where the child should be treated. Children and parents are nowadays actively involved in treatment. The blood glucose monitoring and adjusting of the insulin dose are both done at home. Therefor skills, confidence and autonomy in the management of diabetes are achieved. Specialized diabetes nurses provide guidance to patients in self-monitoring and self-management (Franklin SL, et al. 2000). Optimal regulation of diabetes will minimize the need for hospital admission. Is initial hospital care "really" more required than home care?

2 Aim

The aim is to calculate the incidence during 1996-1999. A comparison will be made with previous results: those of 1978-1980 (Vaandrager GJ, 1984), 1988-1990 (Hirasing RA, 1995), and 1993-1995 (Reeser HM, 1998). We will compare the incidence in the age groups 0-4, 5-9 and 10-14 year olds.

Secondly, the initial treatment management will be analyzed. The initial treatment applied; namely home to hospital based, will be compared to several aspects of the clinical presentation.

3 Method

3.1 Information gathering

3.1.1 Primary Source

A nation-wide register, the Dutch Pediatric Surveillance Unit (DPSU), has been operational since October 1st 1992. The DPSU is a project of the Pediatric Association of the Netherlands, implemented by TNO. All practicing pediatricians in the Netherlands are asked monthly to report new cases of a few selected diseases, diabetes being one of them. The set up of this type of registration is defined by the following:

- Target population:
  The total child population residing in the Netherlands.
- Data collection:
  Pediatricians state monthly on blue registration cards (Appendix A) the child's birth date, initials and month in which diabetes type 1 is diagnosed. These cards are returned to TNO. Upon receiving the registration cards, DPSU sends out questionnaires (Appendix B) related to the child's family and medical history, its clinical condition and the initial treatment at diagnosis. When filled in the questionnaires are returned and analyzed. The questionnaires are subjected to inclusion and exclusion criteria.
  A more extensive, regional project (Kolibri) is incorporated into the DPSU. This cooperation project deals with the children in the province of South Holland. It operated between January 1995 and December 1999. Kolibri questionnaires (Appendix C) resembling the DPSU questionnaires, were sent. A consent form was attached to collect blood and information of the children who were newly diagnosed in this region, as well as from their parents and siblings. The combined questionnaires (Kolibri and DPSU) were analyzed to create this nation-wide study. They are the DPSU primary source. The cards and questionnaires are cleaned for possible duplicates by comparing initials, date of diagnosis, postal codes, and residence to all identical birth dates. To increase accuracy the days and months of birth were also momentarily switched to double check. The cleaned primary source is then stored in a SPSS program to be analyzed.
- Questionnaire criteria:
  Inclusion criteria are defined as: 1) Age at first insulin injection <15 years, 2) Permanent inhabitant of the Netherlands at the moment of the first insulin injection, and 3) Permanent dependency of insulin. While exclusion criteria are specified as: 1) Diabetes secondary to other diseases, for example cystic fibrosis, thalassemia, 2) Insulin resistance syndromes, and 3) Specific syndromes such as Down, Turner or Prader-Willi syndrome.

3.1.2 Secondary Source

Independent of the primary DPSU source, the Dutch Diabetes Association (DDA) has been approached. The DDA is a patient organization where diabetics or parents can receive information as well as support. The DDA was supplied with a compact questionnaire (Appendix D) for its members. New members are regularly asked to send this questionnaire with consent form to TNO. The questionnaire contains the child's name, birth date, date of the first insulin injection, name of treating pediatrician and hospital. Initials, date of diagnosis, postal codes, and residence were compared to all

identical birth dates. The entries of the secondary source were also scrutinized, to weed out any possible DDA duplicates.

3.2 Ascertainment

The combined databases of the primary and secondary sources are used to attain accuracy by the capture-recapture method. This is used to estimate the completeness of the DPSU register by its ascertainment percentage. Hence the incidence and its 95% confidence interval are calculated.

Ascertainment is calculated using a 2 x 2 table:

		Secondary source: Yes	Secondary source: No
Primary source: Yes		a	b
Primary source: No		c	$d = x$

a = number of cases in both registers
b = number of cases in primary source only (DPSU register)
c = number of cases in secondary source only (DDA register)
d = number of cases in neither primary nor secondary source

The total sum of cases is $a + b + c + d$. The total sum of observed cases is $a + b + c$, being under all circumstances the lowest possible lower limit of the confidence interval of the estimated number of cases ("ascertainment adjusted rate"). According to some (Hamman RF, et al. 1990), d can also be written as equation {1}:

$$d = bc / a \qquad \{1\}$$

After correction for small samples the total nearly unbiased estimate of cases in the population is:

$$\text{P NUE} = \frac{(a+b+1)(a+c+1)}{a+1} - 1 \qquad \{2\}$$

When we substitute in equation {2} for:
$a + b = \mathbf{M}$ = the total cases in primary source (DPSU)
$a + c = \mathbf{n}$ = the total cases in secondary source (DDA)
$a = \mathbf{m}$ = the total cases in both databases

The total number of cases $\mathbf{N}$ (= P NUE) can also be written by equation {3}:

$$\mathbf{N} = \frac{(\mathbf{M}+1)(\mathbf{n}+1)}{(\mathbf{m}+1)} - 1 \qquad \{3\}$$

Others (Bishop YMM, et al. 1975) have estimated the variance of N using the equation:

$$\text{Var}(N) = \frac{(M+1)(N+1)(M-m)(n-m)}{(m+1)^2(m+2)} \quad \{4\}$$

The (symmetrical) 95% confidence interval can then be calculated:

$$95\%\ \text{CI} = \pm 1.96 \sqrt{\text{var}(N)} \quad \{5\}$$

The completeness of ascertainment (Hamman RF, et al. 1990) is calculated from the following equation:

$$(a+b+c) / [a+b+c+(bc/a)] \quad \{6\}$$

which can also be written as equation {7}: {7}

$$\text{Ascertainment} = \frac{a(a+b+c)}{(a+b)(a+c)}$$

3.3 Incidence

The total number of children in the Netherlands during the period 1996-1999 is attained through Statistics Netherlands, Voorburg and Heerlen (Statistics Netherlands CBS, 2000). The children are divided into different age groups: 0-4 years, 5-9 years, and 10-14 years. The period 1996-1999 is examined in this study. In order to correct the four year incidence period for possible increase and decrease of the total number of children in the study period, the total number of children in 1996 and the year after the study 2000 are added with twice the total number of children in 1997, 1998 and 1999. The total number is then divided by 8, to estimate an accurate number of children residing in the Netherlands during the study period. The calculated number of cases and its variance divided by the total number of children, provide the incidence per 100,000/year with its confidence interval. Incidences for each separate year from 1996 to 1999 were calculated using only the corresponding CBS yearly population data.

3.4 Incidence increase

The incidence increase over a specific time interval is calculated by subtracting the newly estimated incidence with previously established incidences. The annual increase between the first national incidence study of 1978-1980 and the present one is measured. Therefore the incidence established over a given study period is noted as the incidence of its midpoint; e.g. during 1978-1980 the midpoint is 1979 and during this study 1996-1999 the midpoint is 1997.5. The difference in incidence is divided by the years between the midpoints to generate the increase per annum: supplementary cases per 100,000/year. The increase is also calculated, dividing the difference in incidence first by the original incidence as estimated in the first study (1978-1980), then by the interval of years spread (midpoints) multiplied by 100%, generating the relative annual increase rate.

3.5 Ratio of incidence for the youngest age group

The ratio between the incidence in the youngest age group studied, the children of 0-4 years, and the incidence in the overall group 0-14 years, is calculated by equation {8}:

$$\text{Ratio of incidence} = \frac{\text{incidence for youngest age group}}{\text{incidence 0-14 year olds}} \quad \{8\}$$

3.6 Characteristics of the newly diagnosed child with diabetes type 1

From the questionnaires received at TNO before January 2001, the data were used for analysis. The age for each individual was calculated by subtracting the date of reported first insulin injection from the date of birth. The mean age at presentation was computed. The gender of the child was retrieved from the questionnaires and the male:female ratio was calculated dividing the total number of boys by the total number of girls. The ethnicity of the child was recovered from the questionnaires stating the maternal country of origin.

3.7 Clinical presentations of the newly diagnosed child with diabetes type 1

The general clinical presentation consists of symptoms scored and reported by the treating pediatricians, as well as the laboratory results correlated to the illness. The symptoms observed reflect the child's consciousness (normal, decreased or comatose) and hydration status (decreased or normal). The reported laboratory values included serum glucose level, blood pH value, and presence of ketonuria. The various aspects of the general clinical condition were also compared to the initial treatment the child received; home versus hospital based.

3.8 Statistical methods

The statistical significance of the variables is analyzed using the chi-square test in the SPSS 10.0 program. A p-value < 0.05 is considered significant.

4 Results

4.1 Information gathering

The DPSU received 1,714 diabetes registration cards in connection with the period studied (1996-1999). It appeared a total of 240 cards were duplicate registrations: the same patient was reported twice. Only one patient was reported thrice. After cleaning 1,592 patients were suitable to enter the study. Furthermore, duplicate cards led to a number of duplicate DPSU questionnaires that were rejected. During the final cleaning another 20 duplicate questionnaires with identical data were discovered and one of each pair have been discarded. The DPSU questionnaires suitable to analyze amounted to 1,284. The DPSU questionnaire response is 81% of the registrations received by card. TNO received also 896 DDA questionnaires. A total of 137 had to be refused, because the reported patients had developed diabetes outside the study period (1996-1999) or were $\geq$15 years of age at the moment of diagnosis, providing 759 suitable ones.

4.2 Ascertainment

The numbers of questionnaires involved in this study, arranged by source and age of the newly diagnosed child with diabetes type 1, and the calculated ascertainment to estimate the completeness of the DPSU register applying equations {6} and {7} are given in Table 1.

Table 1 Number of DPSU and DDA diabetes type 1 questionnaires suitable to analyze, arranged by age group, and the corresponding ascertainments as determined, over the period 1996-1999

Age Group	DPSU	DDA	Both	Ascertainment %
0-4 years	331	214	140	80
5-9 years	454	306	182	76
10-14 years	499	239	132	67
All, 0-14 years	1,284	759	454	74

4.3 Incidence

The total number of cases and its variance using equation {3} and {4} was calculated during the period 1996-1999. The accurate number of children residing in the Netherlands during the study period is ordered by age in Table 2. This results in the calculated incidence per 100,000/year and its 95% confidence interval. The incidence was measured over a four-year period. In Table 3, the incidence is also specified per calendar year in the total group (0-14 years) and youngest age group (0-4 years).

Table 2 The calculated total number of cases of newly diagnosed children with diabetes type 1, the population background in the Netherlands and the corresponding incidence per 100,000/year with its 95% confidence interval (CI), over the period 1996-1999

Age Group	Total Number of Cases	Population Size	Incidence (95% CI)
0-4 years	505 (± 37.1)	975,149	12.9 (12.0 - 13.9)
5-9 years	762 (± 54.2)	985,159	19.3 (18.0 - 20.7)
10-14 years	901 (± 87.4)	928,910	24.2 (21.9 - 26.6)
All, 0-14 years	2,145 (± 100.3)	2,889,219	18.6 (17.7 - 19.4)

Table 3 Incidence of diabetes type 1 per 100,000/year with its 95% confidence interval (CI) per calendar year, in the total and youngest age groups

Year	Age Group, 0-4 years (95% CI)	All, 0-14 years (95% CI)
1996	9.5 (8.6 - 10.6)	18.5 (16.7 - 20.3)
1997	11.9 (10.5 - 13.3)	18.2 (16.5 - 19.9)
1998	14.8 (12.6 - 17.0)	19.8 (18.2 - 21.4)
1999	15.8 (12.8 - 18.9)	18.2 (16.5 - 19.9)
1996-1999	12.9 (12.0 - 13.9)	18.6 (17.7 - 19.4)

4.4 Incidence increase

The incidence increase between 1978-1980 and 1996-1999 is specified in Table 4. The additional number of newly diagnosed children with diabetes type 1 in comparison to the first nation-wide incidence study is shown by increase per annum in cases per 100,000/year, as well as its relative annual increase percentage.

Table 4 Incidence and its 95% confidence interval (CI) of diabetes type 1 according to age groups over the periods 1978-1980 and 1996-1999, with its absolute and relative increases per year

Age Group	1978-1980 (95% CI)	1996-1999 (95% CI)	Supplementary Cases per 100,000/year	Relative Increase per annum
0-4 years	6.8 (6.6 - 7.1)	12.9 (12.0 - 13.9)	0.33	4.8 %
5-9 years	10.9 (10.3 - 11.6)	19.3 (18.0 - 20.7)	0.45	4.2 %
10-14 years	14.3 (10.5 - 11.7)	24.2 (21.9 - 26.6)	0.54	3.7 %
All, 0-14 years	11.1 (10.5 - 11.7)	18.6 (17.7 - 19.4)	0.41	3.6 %

4.5 Ratio of incidence for youngest age group

The ratio of incidence from data of previous studies (1978-1980, 1988-1990 and 1993-1995) are calculated applying equation {8} and shown as a reference with the present results in Table 5.

Table 5 Ratio of incidence between the youngest age group 0-4 years and the overall group 0-14 years

Year	Age Group, 0-4 years	All, 0-14 years	Ratio of Incidence (0-4 / 0-14)
1978-1980 *	6.8	11.1	0.61
1988 **	6.9	11.0	0.63
1989 **	5.6	11.6	0.48
1990 **	6.9	12.1	0.57
1988-1990 *	6.4	12.4	0.52
1993 **	11.6	14.8	0.78
1994 **	11.2	12.7	0.88
1995 **	11.3	15.1	0.75
1993-1995 **	11.4	14.2	0.80
1996	9.5	18.5	0.51
1997	11.9	18.2	0.65
1998	14.8	19.8	0.75
1999	15.8	18.2	0.87
1996-1999	12.9	18.6	0.69

* Hirasing RA, et al. 1996, ** Reeser, HM 1998

4.6 Characteristics of the newly diagnosed child with diabetes type 1

The mean age of the newly diagnosed child with diabetes type 1 is 7.6 (95% CI 7.4 - 7.9) as calculated from the total number of 1,284 DPSU questionnaires analyzed. In previous years the mean age was measured as 8.0 (7.8 - 8.3) in 1993-1995 and 9.2 (9.0 - 9.5) in 1988-1990.

4.6.1 Gender dependence

The gender dependence was observed with the male to female ratio in Table 6. A total of 1,284 questionnaires in this study were returned of which 1,282 contained the required gender information. In the previous incidence studies the male:female ratio was 0.93 in 1993-1995 and 0.99 in 1988-1990 (Reeser HM, 1998).

Table 6 Gender ratio in newly diagnosed children 0-14 year with diabetes type 1 over the period 1996-1999

Year	Male, n (%)	Female, n (%)	Male: Female Ratio
1996	168 (52)	157 (48)	1.07
1997	175 (55)	145 (45)	1.21
1998	176 (51)	168 (49)	1.05
1999	145 (49)	149 (51)	0.97
1996-1999	664 (52)	618 (48)	1.07

4.6.2 Descent

The ethnicity of the child was recovered from the questionnaires stating the maternal country of origin. Twenty questionnaires were excluded due to missing information concerning this issue. A total of 1,264 questionnaires were analyzed. A variety of countries of origin were reported each less than 4 times equaling a total of 66 questionnaires (5.2 %). These various countries were not separately stated in Table 7.

Table 7 The reported country of origin of the newly diagnosed child with diabetes type 1 as specified for its mother

Country of Origin	Number	%
the Netherlands	1,081	84.2
Morocco	63	4.9
Surinam	19	1.5
Turkey	15	1.2
Somalia	10	0.8
Dutch Antilles and Aruba	4	0.3
Various countries	72	5.7

4.7 Clinical presentations of the newly diagnosed child with diabetes type 1

4.7.1 *General clinical presentations*

The general clinical presentation consists of the symptoms scored by the pediatricians and the laboratory results reported. For the total population studied, the information retrieved from the questionnaires per item as well as the relative subdivision as a percentage is given in Table 8.

Table 8 General clinical presentations scored and the relative subdivisions of the newly diagnosed children with diabetes type 1 over the period 1996-1999

Clinical presentation	Number reported	Percentage reported
Consciousness	1,123	
normal	976	86.9
decreased	126	11.2
comatose	21	1.9
Hydration status	1,109	
normal	709	63.9
decreased	400	36.1
Serum glucose	1,239	
≤ 11.0 mM	17	1.4
> 11.0 mM	1,222	98.6
Blood pH	1,123	
< 7.33	322	28.7
7.34 - 7.45	774	68.9
> 7.45	27	2.4
Ketonuria	1,092	
presence	746	68.3
absence	346	31.7
Initial treatment	1,250	
home based	188	15.0
hospital based	1,062	85.0

4.7.2 *Clinical presentations and age distribution*

The general clinical presentations scored by the pediatricians and the laboratory results reported are shown per age group in Table 9. Statistical analysis with the chi square

showed in the age group 0-4 years significant differences in consciousness (more children had decreased consciousness or were comatose), as well as the lower mean blood pH values. In the age group 5-9 years the presence of ketonuria was significantly higher.

Table 9 Clinical presentations, mean values and 95% confidence intervals (CI) per age group of the newly diagnosed children with diabetes type 1 over the period 1996-1999

	0-14 (n = 1,263)	0-4 (n = 329)	5-9 (n = 452)	10-14 (n = 482)	*p*- value
Consciousness					
# scored (%)	1,123 (87.5)	294 (89.4)	393 (86.9)	428 (88.8)	0.002*
Decreased (%)	11.2	13.9	7.6	12.6	
Comatose (%)	1.9	3.4	0.5	2.0	
Hydration status					
# scored (%)	1,109 (87.8)	288 (87.5)	390 (86.3)	423 (87.8)	0.475
Decreased (%)	36.1	37.2	33.3	38.1	
95% CI	33.9 - 38.6	35.2 - 39.8	31.2 - 35.9	36.0 - 40.6	
Duration symptoms					
# scored (%)	951 (75.2)	254 (77.2)	339 (75.0)	351 (72.8)	0.323
Mean, days	21.3	16.7	20.3	24.8	
95% CI	19.5 - 23.1	14.9 - 18.5	17.3 - 23.2	21.5 - 28.0	
Serum glucose					
# scored (%)	1,239 (98.1)	319 (96.9)	440 (97.3)	472 (97.9)	0.164
Mean, mM	30.6	32.6	30.5	29.5	
95% CI	29.8 - 31.4	31.1 - 35.6	29.7 - 32.9	28.5 - 31.0	
Blood pH					
# scored (%)	1,124 (88.9)	295 (89.7)	420 (92.9)	421 (87.3)	0.027*
Mean	7.34	7.33	7.35	7.34	
95% CI	7.33 - 7.34	7.31 - 7.34	7.34 - 7.37	7.32 - 7.35	
< 7.30 (%)	19.6	21.4	14.5	20.2	
< 7.20 (%)	9.5	14.2	7.1	11.6	
Presence of ketonuria					
# scored (%)	1,092 (86.5)	269 (81.8)	395 (87.4)	419 (86.9)	0.005*
Positive (%)	68.3	63.2	65.8	50.1	
95% CI	67.6 - 69.0	62.6 - 63.9	65.2 - 66.5	49.4 - 50.9	

* Significantly different by chi square analysis

4.8 Initial treatments related to clinical presentations

The various aspects of the clinical symptoms and laboratory evaluation are compared to the setting of treatment that the children underwent. They were either admitted to the hospital or regulated at home on an outpatient basis. In Table 10 a comparison of consciousness, hydration status, mean serum glucose level and blood pH value, and the presence of ketonuria is made between those children regulated at home or in the hospital. Of the total amount of children scored (n=1,250), 21 children were comatose (9 of them were < 5 years old) and all were hospitalized (2%). Of the lethargic children, 126 in number, only 103 were hospitalized and 23 regulated at home (p <0.0001). A decreased hydration status was observed in 400 children, 380 were hospitalized and 20

regulated at home (p <0.0001). The mean serum glucose level and blood pH value showed no significant difference to the initial treatments: home or hospital based. Ketonuria was present in 746 children of whom 656 were hospitalized and 90 regulated at home (p <0.0001).

Table 10 Clinical presentations compared with initial treatments given to the newly diagnosed children 0-14 years with diabetes type 1 over the period 1996-1999

Clinical Presentations	Initial Treatments		p-value
	Home based	Hospital based	
Consciousness			<0.0001*
Normal	88%	11%	
	12%	87%	
Hydration status			<0.0001*
Normal	89%	59%	
Decreased	11%	41%	
Serum glucose, mean values mM	25,4	32.0	0.541
Blood pH, mean values	7,39	7,34	0.309
Ketonuria			<0.0001*
Presence	48%	72%	
Absence	52%	38%	

* significantly different by chi square analysis

The choice of initial treatment is separately compared, successively with the age distribution, intervals of the serum glucose level and blood pH value of the newly diagnosed child with diabetes type 1 (Figures 1, 2 and 3).

4.8.1 *Initial treatment related to age distribution*

In 1,241 questionnaires both items, the place of initial treatment and the age of the child, were supplied. A total of 325 questionnaires concerned children aged 0-4, 445 children were 5-9 and 471 were 10-14 years old (Figure 1).

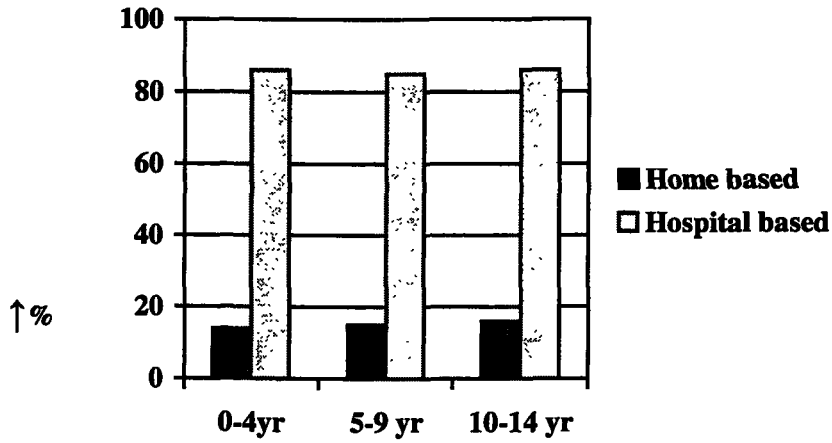

Figure 1 *The initial treatment given to the newly diagnosed children with diabetes type 1 over the period 1996-1999 according to age at moment of diagnosis*

4.8.2 *Initial treatment related to serum glucose level*

In 1,222 questionnaires both items, the place of initial treatment and the serum glucose level, were supplied. A total of 17 questionnaires concerned children with serum glucose levels ≤ 11 mM, and 1,208 children had serum glucose levels >11 mM (Figure 2).

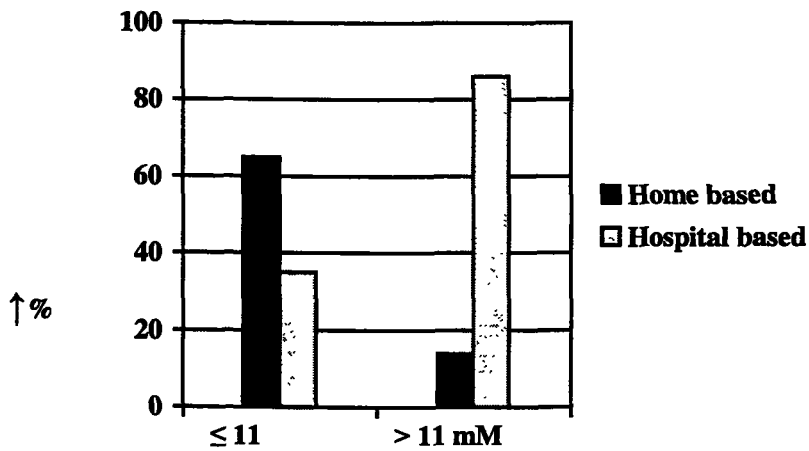

Figure 2 *The initial treatment given to the newly diagnosed children with diabetes type 1 over the period 1996-1999 according to serum glucose level*

4.8.3 *Initial treatment related to blood pH value*

In 1,110 questionnaires both items, the place of initial treatment and the blood pH value, were supplied. A total of 318 questionnaires concerned children with blood pH values < 7.33, 765 children had values between 7.34 and 7.45, and 26 children had values > 7.46 (Figure 3).

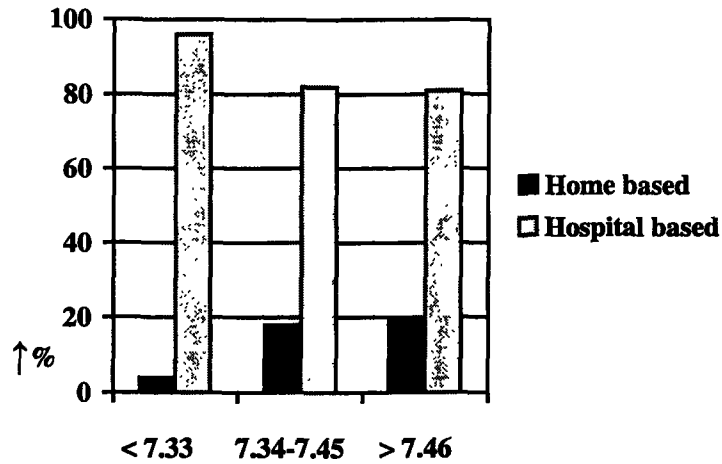

Figure 3 The initial treatment given to the newly diagnosed children with diabetes type 1 over the period 1996-1999 according to blood pH value

5 Discussion

5.1 Information gathering

Completeness of the register is achieved through the capture-recapture method (Hook EB and Regal RR, 1992), correcting for any non-registrations as well as non-reports. The method used to measure the incidence throughout the years was identical. The execution has changed. In the first two incidence studies of 1978-1980 and 1988-1990 data was obtained from pediatricians and internists, while during 1993-1995 and 1996-1999 data originated form the newly founded DPSU. The DPSU operates using registration cards and questionnaires. A total of 1,714 registration cards referred to 1,592 newly diagnosed children and yielded 1,284 suitable questionnaires. The questionnaire response is 81%. The response was 94% in the previous incidence study (Reeser HM, 1998). For the establishment of the incidence, registration of patients by the cards suffices and its results are more accurate. In order to increase accuracy we therefore substitute for the DPSU questionnaires, the registration cards as our primary source and obtain an alternative ascertainment (Table 11) as well as incidence (Table 12). The results from this alternative for the primary source are compared to the original results (Table 13).

5.2 Ascertainment

Table 11 Number of DPSU registration cards and DDA diabetes type 1 questionnaires suitable to analyze, arranged by age group, and the corresponding alternative ascertainments as determined over the period 1996-1999

Age Group	DPSU	DDA	Both	Ascertainment %
0-4 years	405	214	164	86
5-9 years	561	306	206	79
10-14 years	626	239	161	76
All, 0-14 years	1,592	759	531	80

5.3 Incidence

Table 12 The calculated total number of cases from the DPSU registration cards of newly diagnosed children with diabetes type 1, the population background in the Netherlands and the corresponding alternative incidence per 100,000/year with its 95% confidence interval (CI), over the period 1996-1999

Age Group	Total number of cases	Population size	Incidence (95% CI)
0-4 years	528 (± 29.8)	975,149	13.5 (12.7 - 14.3)
5-9 years	832 (± 51.5)	985,159	21.2 (23.1 - 20.4)
10-14 years	928 (± 70.0)	928,910	25.0 (23.1 - 26.9)
All, 0-14 years	2,274 (± 86.0)	2,889,219	19.7 (18.9 - 20.4)

Table 13 Comparison of the alternative and original incidence of diabetes types 1 in children 0-14 years old per 100,000/year with its 95% confidence interval (CI) depending if DPSU registration cards or questionnaires are used as the primary source

Year	Total number of cases and Ascertainment				Incidence (95% CI)	
	Registration cards		Questionnaires		Registration cards	Questionnaires
1996	544 ± 46	79 %	526 ± 51	70 %	19.1 (17.5 - 20.7)	18.5 (16.7 - 20.3)
1997	554 ± 42	81 %	520 ± 49	74 %	19.4 (17.9 - 20.8)	18.2 (16.5 - 19.9)
1998	607 ± 43	80 %	571 ± 47	80 %	21.1 (19.6 - 22.6)	19.8 (18.2 - 21.4)
1999	560 ± 40	81 %	531 ± 50	73 %	19.2 (17.8 - 20.6)	18.2 (16.5 - 19.9)
1996-1999	2,274 ± 86	81 %	2,145 ± 100	74 %	19.7 (18.9 - 20.4)	18.6 (17.7 - 19.4)

The incidence measured from the registration cards is approximately 5% higher then that of the questionnaires (Table 13). The advantage of the DPSU registration cards as the primary source may overcome the inaccuracy caused by the 81% response of the DPSU questionnaires explaining the smaller confidence interval of the incidence: a range of 1.5 for 19.7 compared to a range of 1.7 for 18.6. However, the registration cards do not provide the exact moment of first insulin injection whereby the age of the newly diagnosed child can be precisely calculated. Furthermore, when reliably comparing the increase of diabetes incidence over time, identical methods must be used in both studies. Therefore we reject this change of method, however the prerequisite should be explored for future studies. It saves effort and increases accuracy.

5.4 Incidence increase

The incidence annual increase rate compared to 1978-1980 for each study performed is specified in Table 14. The annual increase rate is highest after 1988-1990 in the children aged 0-4 years. This increase during a short period of time insinuates an environmental contribution of diabetes type 1 (Åkerblom HK and Knip K, 1998) with higher susceptibility in the children of the youngest age groups. Since 1993-1995 the incidence increase of diabetes type 1 further augments. More children seem to become susceptible to the environmental factor(s) that causes the disease to manifest at younger age.

Table 14 Incidence of diabetes type 1 according to age group over the periods 1988-1990, 1993-1995 and 1996-1999, with its relative annual increase rate compared to 1978-1980 (%)

Age Group	1988-1990	1993-1995	1996-1999
0-4 years	6.4 (-0,6%)	11.4 (4.5%)	12.9 (4.8%)
5-9 years	12.4 (1.4%)	14.5 (2.2%)	19.3 (4.2%)
10-14 years	18.1 (2.7%)	17.1 (1.3%)	24.2 (3.7%)
All, 0-14 years	12.4 (1.2%)	14.2 (1.9%)	18.6 (3.6%)

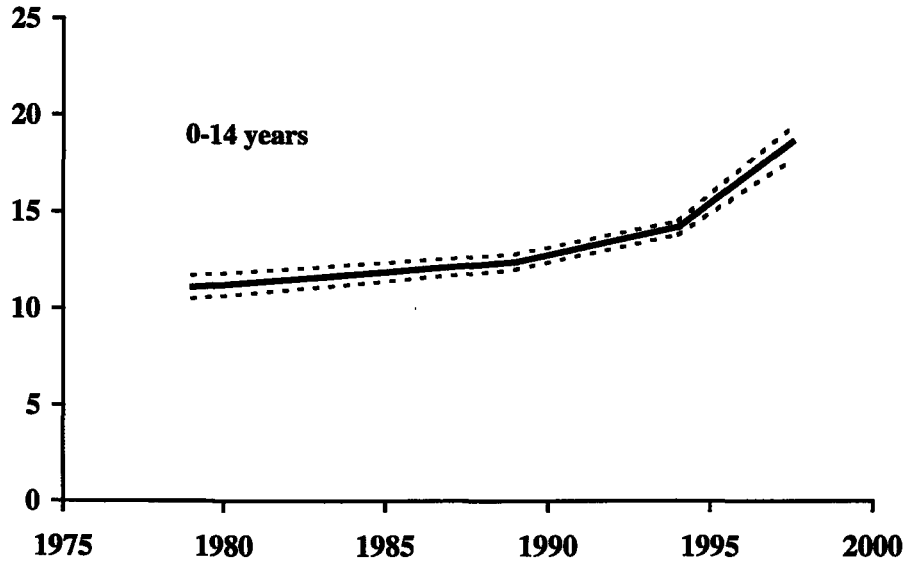

Figure 4 Incidence per 100,000/year and its 95% confidence interval (CI) of diabetes type 1 in children 0-14 years old over the periods 1978-1980, 1988-1990, 1993-1995 and 1996-1999

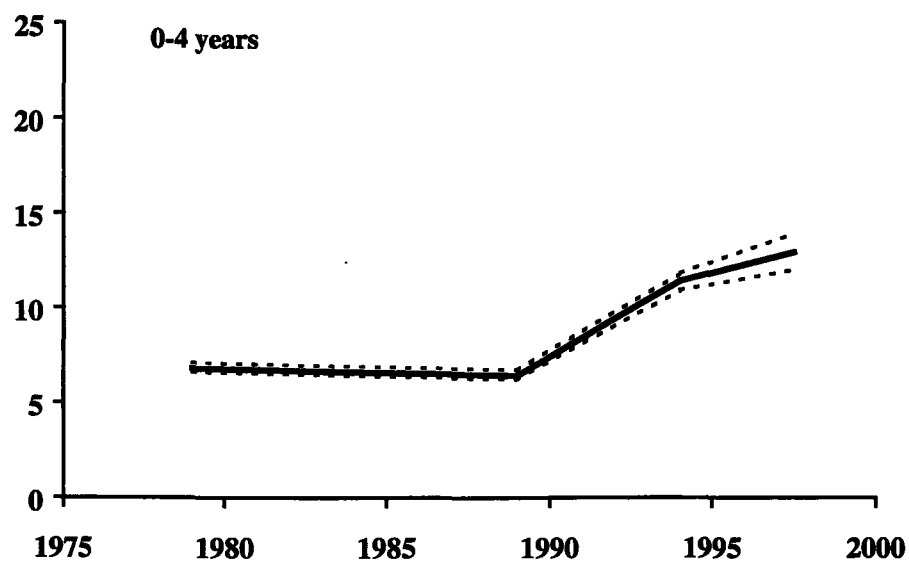

Figure 5 Incidence per 100,000/year and its 95% confidence interval (CI) of diabetes type 1 in the youngest age group, the children 0-4 years old over the periods 1978-1980, 1988-1990, 1993-1995 and 1996-1999

5.5 Ratio of incidence for the youngest age group

The increase of the incidence differs between the age groups studied. The relative increase from 1978-1980 till 1996-1999 is highest in the children < 5 years of age (Table 4). The ratio of the incidences for the youngest age group to the combined groups varies between 0.48 and 0.88 in the period under study and in the previous periods studied (Table 5). More children develop diabetes, at younger ages, and as these effects coincide in the population they influence the pattern of the diabetes incidence not equally causing the ratio to fluctuate. Sharp fluctuations within a fixed range during a short time interval support the contribution of environmental influence in the development of diabetes type 1. The susceptibility at different age varies over time.

5.6 Characteristics of the newly diagnosed child with diabetes type 1

Linear regression of the mean age of the newly diagnosed child with diabetes type 1 from 1988-1990 to 1996-1999 shows the mean age to decrease by -0.19 age year per calendar year (r -0.98). By extrapolation the mean age of the newly diagnosed child will theoretically decrease to 0 years of age after 25 years. This exercise merely stresses the importance even of the intrauterine period within the ontogenesis of childhood diabetes. Hence environmental influence on the pregnant mother needs to be included in studies to elucidate the causes of childhood diabetes. The gender of the child is of no importance in these studies, while the origin of the family of the child with diabetes appears to be prominent and calls for the study of the environment of our society and within the family.

5.6.1 Gender dependence

During 1996-1999 the male:female ratio in the total population aged 0-14 years old was 1.05 (Statistics Netherlands CBS, 2000). In the children with diabetes the ratio was equally 1.07. The disease equally affects boys and girls.

5.6.2 Descent

Reliable incidence estimates for diabetes type 1 on ethnicity can not be obtained. We therefore comment on the available data from the DPSU. From 1,264 DPSU questionnaires the ethnicity of the child was recovered. These children with diabetes have been identified during the period 1996-1999. The total population of children aged 0-14 years old during this period has been accounted for (Statistics Netherlands CBS, 2000). An estimated number of 11 children/100,000 were identified by the DPSU questionnaires during 1996-1999 with diabetes type 1. The number of first and second-generation foreign residents according to Statistics Netherlands was also accounted for during the years 1996-1999. The total numbers of these populations from the countries specified in Table 7 were computed. The identified children/100,000 during 1996-1999 were then determined for each country of origin. These results are shown in Table 15 only for comparison. The increased number of children from Somali and Moroccan descent is distinct. Rising numbers of children that develop diabetes type 1 characterizes migration from these African countries to the Netherlands. Migration from Turkey, Surinam, the Dutch Antilles and Aruba to the Netherlands is not characterized by these higher numbers of diabetes type 1. After migration from a lower diabetes incidence country to a country with higher incidence, the incidence in the migration population gradually approaches the level of the country of residence. The diabetes type 1 incidence pattern after migration from Somalia and Morocco to the Netherlands

shows a pattern contrary to this pattern. These unique phenomena observed, call for an explanation. The environmental changes that the various groups of children have been exposed to with such very different health effects after migration needs to be explored.

Table 15 The children identified with newly diagnosed diabetes type 1 by the DPSU during 1996-1999 (identified cases), the total population first and second generation residents in the Netherlands aged 0-14 years, arranged by their respective countries of origin, and compared per 100,000 (Statistics Netherlands CBS, 2000)

Country of origin	All identified cases during 1996-1999, (n)	Total first and second generation residents aged 0-14 year added during 1996-1999, x 1,000, (N)	Identified cases/100,000 first and second generation residents, (n/N)
All	1,264	11,506	11
the Netherlands	1,081	9,570	11
Morocco	63	342	18
Surinam	19	410	5
Turkey	15	477	3
Somalia	10	37	27
Dutch Antilles and Aruba	4	110	4
Various countries	72	625	12

5.7 Clinical presentations of the newly diagnosed child with diabetes type 1

The results retrieved from questionnaires (Table 8) are compared with those analyzed in the previous study 1993-1995 (Reeser HM, 1998). It is clear that over time more children have normal consciousness according to the treating pediatricians: in 1993-1994 81.2 %, now 86.5 %. The share of children with normal hydration status increased from 56.7 %, to 63.9 %. The corresponding laboratory values reported show similar improvements. The mean serum glucose level decreased form 31.4 mM to 30.6 mM, the mean blood pH value improved from 7.31 to 7.34, and the presence of ketonuria diminished from 72.9% to 68.3%.

5.7.1 General clinical presentations and age distribution

Consciousness and blood pH values in the children 0-4 years were significantly lower compared to the other age groups (Table 9). In this age group more children were either comatose or lethargic and acidic according to the treating pediatricians. The occurrence of ketonuria was significantly higher in children 5-9 years. In the previous study 1993-1995 consciousness at onset was also poorer with younger ages, while difference in blood pH could not be detected between the age groups; positive ketonuria was then more frequent among 10-14 year olds.

5.8 Initial treatment related to clinical presentations

The overall improvement discussed above in 5.7 has coincided with more children initially being treated at home (Table 8). Indeed 15% of the newly diagnosed children stayed at home and had not been admitted into the hospital. In a previous study during 1993 and 1994 (Reeser HM, 1998), this group consisted of just 11%. This increase of home based management for newly diagnosed diabetic children > 2 years is clinically relevant. In a prospective Canadian study initial home treatment resulted three years later in better metabolic control and similar psychosocial outcome (Dougherty G, et al. 1999).

5.8.1 *Initial treatment related to age distribution*

The treatment strategy of the Dutch pediatricians showed little association with age of the newly diagnosed children with diabetes type 1. In all age groups equally, 15% of the children had initially been treated at home (Figure 1). Age does not impede home based management.

5.8.2 *Initial treatment related to serum glucose level*

Initial treatment is correlated with the serum glucose level. Even though in the small sample of children with normal levels (n = 17) the majority are regulated at home, however 6 children were still admitted in hospital (Figure 2). With elevated serum glucose levels the vast majority is admitted. In spite of the elevated serum glucose levels, 169 of the children did receive home based care. Hyperglycemia per se seems not to be a deterrent for home based care.

5.8.3 *Initial treatment related to blood pH value*

Age or serum glucose level appear not to solely influence the choice between home or hospital based care. Ketoacidosis is the most feared complication due to its high mortality. CBS Netherlands has reported no mortality cases during the period 1996-1999 of children with ketoacidosis due to not yet acknowledged diabetes type 1. Still of the children with some signs of ketoacidosis 4% had been successfully managed at home at the moment of diagnosis (Figure 3). The combined influence of serum glucose level and blood pH value is therefore also analyzed. In 1,084 questionnaires both items were supplied. Significantly more hyperglycemic children with lower blood pH value were hospitalized (Table 16).

Table 16 Blood pH value in hyperglycemic children compared to initial treatments given to the newly diagnosed ones 0-14 years with diabetes type 1 over the period 1996-1999

Serum glucose >11mM (n=1,084)	Home based (n=147)	Hospital based (n=937)
pH < 7.33	8% (n=12)	32% (n=299)
pH 7.34 - 7.45	89% (n=130)	66% (n=618)
pH > 7.45	3% (n=5)	2% (n=20)

Significantly different by chi square analysis; p -value < 0.001

5.9 General discussion

The incidence of diabetes type 1 in the Netherlands increases. Between the four Dutch incidence studies, the relative rate of increase mounted from 0.6% to 4.8% (Table 14). Since the first incidence study the average overall increase is 3.6% (Table 4). In the youngest age group the average increase since 1978-1980 reaches 4.8%. Between 1988-1990 and 1993-1995 the relative increase in the children 0-4 years peaked (15.6%). In other countries it is also noticed that the incidence increase peaks. During the same time interval, incidences between countries also differ (Karvonen M, et al. 2000). The incidence for the Netherlands and its neighboring countries estimated during 1990-1994 varies between 11.0 and 17.8 (Table 17). In the age group 0-4 between 6.4 and 14.0: the ratio of incidence fluctuates between 0.48 and 0.80. It has fluctuated in our country from 1978-1980 on between 0.48 and 0.88 (Table 5).

Table 17 Incidence of childhood diabetes type 1 per 100,000/year during 1990-1994 by country in the total and youngest age groups with its ratio of incidence (data from the EURODIAB ACE study)

Country	Age Group, 0-4 year	All, 0-14 year	Ratio of incidence (0-4 / 0-14)
Belgium, Antwerp	6.4	11.6	0.55
Luxembourg	8.9	11.4	0.78
Germany, Baden-Würtemberg	7.1	11.0	0.65
Denmark	7.5	15.5	0.48
England, Oxford	14.0	17.8	0.79
England, Plymouth	13.9	17.3	0.80
the Netherlands, 5 regions	9.5	13.0	0.73

(Karvonen M, et al. 2000)

The overall increase of the incidence between 1978-1980 and 1996-1999 is compared with available data from the literature: Sweden (Dahlquist G and Mustonen L, 2000) and Hungary (Gyürüs É, et al. 1999). The incidences measured in this period of 20 years correspond to those measured before and predict those for the future (Figures 6 and 7).

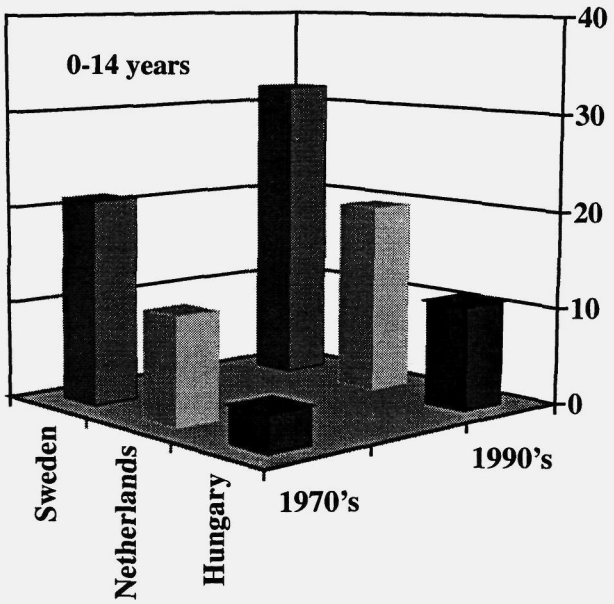

Figure 6 *The comparison of the incidence of diabetes type 1 in children 0-14 years during 1978-1980 1996-1999 in the Netherlands with results from the paralel periods in other countries*

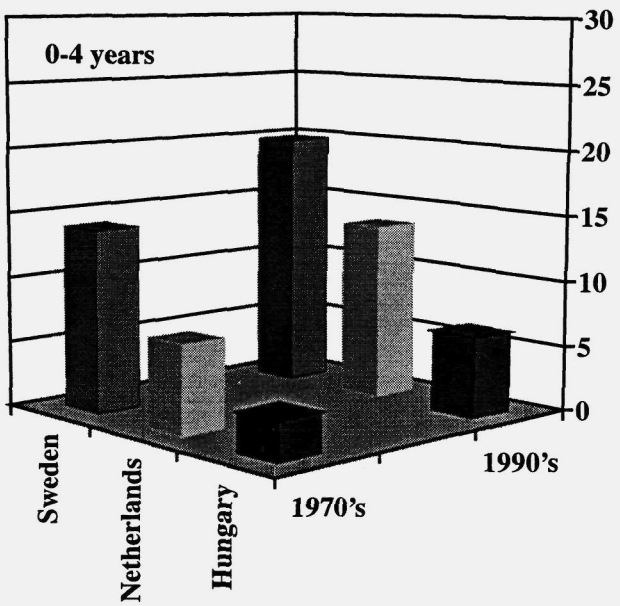

Figure 7 *The comparison of the incidence of diabetes type 1 in the youngest children 0-4 years during 1978-1980 and 1996-1999 in the Netherlands with results from paralel periods in other countries*

There is growing support, however no hard evidence, that several events at the moment of birth or during infancy are related with this increasing diabetes incidence. Numerous factors each and combined are variably associated with this increase. The occurrence of diabetes type 1 has indeed been associated with e.g. low vitamin D status (Cantorna MT, 2000) and deficient Zn status (Haglund B, et al. 1996). Since nutrition has such a central role in fetal life and seems a central stimulus for programming of susceptibility for disease later in life, we hypothesize that disruption of timing and imbalance of nutrients during pregnancy and infancy is a first step in the manageable risk for childhood diabetes.

Breastfeeding and proper weaning are protective and equally important for appropriate colonization of the gastrointestinal tract and subsequently for the well functioning of the mucosal immunity. Mucosal surfaces are favored as portals of entry by viruses or antigens like β-casein from cow's milk (Grönlund M-M, et al. 1999). Intact mucosal immunity is a likely factor to hinder the action of the cell membrane components, the HLA molecules, to present different types of antigen to the T lymphocytes. The destructive cellular reaction at the root of autoimmune disease may than be prevented. Diabetes type 1 and other autoimmune diseases, like autoimmune thyroid disease (Hunter I, et al. 2000), are increasingly the result of these reactions. We hypothesize that damage to the mucosal immunity is a second step in the risk for childhood diabetes. Safeguarding the intact mucosal immunity form birth on may be of protective value.

For diabetes type 1 it is also relevant that human milk contains significantly higher concentrations of insulin, compared to low concentrations in cow's milk and absent values in most infant formulas (Shehadeh H, et al. 2001). Oral insulin promotes intestinal maturation and may prevent diabetes type 1 directly or indirectly. Oral insulin tolerance is now clinically tested on its impact to prevent diabetes type 1, as is oral tolerance in several other autoimmune diseases. Precise dosing and timing of the antigen like insulin, is the key to be determined in order to effectively prevent the destructive cellular autoimmune reaction by immune modulation in diabetes type 1 (Krause I, et al. 2000). Mucosal maturation and intact mucosal immunity are relevant issues to be included for the correct interpretation of the results in these oral tolerance experiments. A medical history also, is not complete without appropriate recall of the duration of breastfeeding. We hypothesize that exposition to oral insulin in human milk is a third step for the prevention of early development of diabetes type 1.

Many other gastrointestinal processes affect the mucosal immunity directly or indirectly and are associated with the risk for diabetes type 1; e.g. hereditary catalase deficiency (Góth L and Eaton JW, 2000), other forms of oxidative stress (Matteucci E and Giampietro O, 2000), and intestinal lactase activity (Meloni G, et al. 2001). The gastrointestinal tract functions as a barrier against antigens, being promoted by microflora that normalizes increased permeability and down regulates hypersensitivity reactions. Gut microflora might hold properties for the prevention of autoimmune disease as is proven to be effective in the primary prevention of atopic disease (Kalliomäki M, et al. 2001). Indigenous microflora have specific and very different immune modulator properties (Isolauri E, et al. 2001). The role of the intestinal microflora on the immune system is vast and only partially understood (Waaij D van der, 2001), as is the role of the non inherited self and maternal antigens in this respect (Rood JJ van and Claas F, 2000). As they in various and different ways affect the immune system, their single and combined influences in the development of autoimmune disease like diabetes type 1 are of importance. The presence of diverse and specific

microbes in the commensal gut microflora might be more important than common infectious agents in autoimmune disease prevention. We hypothesize that the presence from birth on of a full and wide range of supportive indigenous microflora is a fourth step in the prevention of diabetes type 1.

Environmental factors associated with the early development of diabetes type 1 are also known to induce some degree of immune modulation, directly or by interaction (Hanson LÅ and Yolken RH, 1999). Not a single environmental factor will be the cause of autoimmune disease like diabetes type 1, more likely a combination of factors that repetitive disrupt the normal development of the gastrointestinal immune system. Partial recovery and repetitive damage to the mucosa increases the susceptibility. The various environmental factors associated with the risk for diabetes type 1 therefore need to be studied combined, with their respective time intervals. Relevant environmental factors are those that are associated with induction of immune modulation and the risk for diabetes type 1. For example: the family history of diabetes, the way of delivery and subsequent success of intestinal colonization, the start and duration of breastfeeding with proper implementation of the advised vitamin D supplementation, appropriate weaning, exposure to pathogens, antibiotics, missing vaccinations or aberrant timing, specific growth pattern for weight and height and the general health. Interpretation of the environmental factors for the immature child during pregnancy and their late effects during infancy may identify the major risk(s) for diabetes type 1. For the prevention strategy of diabetes type 1, timing and balance of nutrients during pregnancy and infancy, intact mucosal immunity, prolonged exposition to oral insulin in human milk, and a full and wide range of supportive indigenous microflora could be critical.

In childhood one can only wait for the disease to manifest itself, and act appropriately by referral to a pediatrician for optimal initial treatment, preferably at home.

6 Conclusions

Rapid increase of childhood diabetes occurs in the Netherlands and has been reported worldwide, with great concern for this progressing epidemic. Other autoimmune diseases show also rising incidences during childhood. The causes of this increasing health issue have not been explained. Since it has occurred over a relative short period of time, genetic predisposition does not explain it. It is the result of changes in environmental risks, by factors or events earlier in life, which may prime immune modulation and initiate the slowly progressing autoimmune phenomena that lead to e.g. diabetes. Through environmental risk factors the genetic predisposition comes gradually to expression. Whatever the precise scientific causes, many more children enter adulthood with health risks and complications, which affect their prospects of life. Studying those with the sharpest diabetes increase and those most severely affected offers the best opportunity to identify the associated environmental factors that set prospects for prevention or postponement of outbreak during childhood. Epidemiological analysis of the data on the youngest children with diabetes and those of migrated mothers, compared to the controls without diabetes, will increase our knowledge into evidence of the causes of this disease. It is urgently needed, before a search for prevention strategies can be initiated. An identical approach by case-control analysis has been applied and led to successful prevention of lung cancer (tobacco smoking related) and neural tube defects in infants (folic acid supplement before conception). For the prevention strategy of diabetes type 1, we hypothesize that timing and balance of nutrients during pregnancy and infancy, intact mucosal immunity, prolonged exposition to oral insulin in human milk, and a full and wide range of supportive indigenous microflora are essential.

Since there are more and younger patients with diabetes, it means that in the future the repercussions of this will even be more severe. The choice of initial management should be reconsidered. The decision seems partly independent of age and severity of clinical presentation. For all age groups, hospital admission is required if clinical symptoms at diagnosis are critical. A considerable overlap between the initial clinical symptoms of the home and hospital treated children in the Netherlands is clear from this study. It can also be interpreted that other issues, besides age or clinical symptoms determine the treatment strategy of the pediatrician, such as most likely geographical distribution and quality of and experience with home care management.

7 Recommendations

To increase the ascertainment of the DPSU, simplification of the means of registration (cards in stead of the complete full questionnaires) should be taken into consideration, because the questionnaire response has decreased.

To increase experience and quality of home based treatment, national guidelines for hospital admittance, to overcome the initial critical period and agreement on feasibility of standard outpatient treatment, are warranted. A pediatric diabetic nurse should always be available also for home visits.

We recommend, in order to test our hypothesis, to evaluate the Dutch environment that the child has been exposed to before the onset of diabetes. This is a first step in a complex process that may lead to effective postponement in the outbreak of this disease during childhood. A link between these environmental aspects in general and in the ethnic group that after a relative short period of acculturation in such a small geographical area as the Netherlands has shown prone to develop diabetes is particularly challenging. Which environmental factors precede the manifestation of diabetes type 1? Which single or combined interactive environmental events, capable to induce different degrees of immune modulation and likely to excel the autoimmune phenomena during early life (prenatal, perinatal, infancy and early childhood) can explain the observed incidence characteristics of diabetes type 1 in Dutch children? We owe it to the children aged 0-4 and the children of Moroccan descent aged 0-14 years that did develop diabetes type 1 in such large numbers, to study these combined aspects in relation to the younger occurrence of diabetes type 1 now: the family history of diabetes, the way of delivery and subsequent success of intestinal colonization, the start and duration of breastfeeding with proper implementation of the advised vitamin D supplementation, appropriate weaning habits, exposure to pathogens, use of antibiotics, delay of vaccinations, growth patterns and the general health. We most urgently need to focus on the prevention strategy. Advice on timing and balance of nutrients during pregnancy and infancy is needed. Also, ways to safeguard the mucosal immunity, to prolong the exposition of the infant gut to oral insulin in human milk, and to establish a full and wide range of supportive indigenous microflora should be measured together for their combined potency to prevent childhood diabetes type 1.

Let's expand this knowledge to make youth a comfortable and an easy lifetime!

8 References

ÅKERBLOM HK, KNIP M. Putative environmental factors in type 1 diabetes. Diabetes Metab Rev 1998:14;31-67.

BELFIORE F, IANNELLO S. Etiological classification, pathophysiology and diagnosis. In: New concepts in diabetes and its treatment. Belfiore F, Mogensen CE (eds). Basel. Karger, 2000.

BISHOP YMM, FIENBERG SE, HOLLAND PW. Discrete multivariate analysis: theory and practice. Cambridge MA: MIT Press, 1975:229-65.

BRUINING GJ, RIDDER M de, BATSTRA M, AANSTOOT HJ, BROEK J van den, BUUREN S van, HIRASING RA, ROEP BO. Association between infant growth before onset of juvenile type 1 diabetes and autoantibosdies to IA-2. Lancet 2000;356:655-6.

CANTORNA MT. Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence? Proc Soc Exp Biol Med 2000:223;230-3.

CHOWDHURY TA, MIJOVIC CH, BARNETT AH. The aetiology of type 1 diabetes. Baillière's Best Pract Res Clin Endocrinol Metab 1999:13;181-95.

DAHLQUIST GG, PATTERSON C, SOLTESZ G. Perinatal risk factors for childhood type 1 diabetes in Europe: the EURODIAB substudy 2 study group. Diabetes Care 1999:22;1698-702.

DAHLQUIST G, MUSTONEN L. Analysis of 20 years of prospective registration of childhood onset diabetes—time trends and birth cohort effects. Acta Pædiatr 2000:89;1231-7.

DORMAN JS, BUNKER CH. HLA-DQ Locus of the human leukocyte antigen complex and type 1 diabetes mellitus: a HuGE Review. Epidemiol Rev 2000:22;218-27

DOUGHERTY G, SCHIFFRIN A, WHITE D, SODERSTROM L, SUFRATEGIU M. Home-based management can achieve intensification cost-effectively in type 1 diabetes. Pediatrics 1999:103;122-8.

MOKADEM N el, MATTIAZZO GF, WOUWE JP van, HIRASING RA. De klinische toestand van Nederlandse en Marokkaanse kinderen in Nederland bij de diagnose van diabetes mellitus type 1. Leiden: TNO-PG, 2000. Publ.nr. 01.106

FRANKLIN SL, GEFFNER ME, KAISERMAN KB. Outpatient management of children with diabetes. West J Med 2000:172;194-6.

GÓTH L, EATON JW. Hereditary catalase deficency and increased risk of diabetes. Lancet 2000:356;1820-1.

GRÖNLUND M-M, LEHTONEN O-P, EEROLA E, KERO P. Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarian delivery. J Pediatr Gastroenterol Nutr 1999:28;19-25.

GYÜRÜS É, GYÖRKŐ B, GREEN A, PATTERSON C, SOLTÉSZ G. A gyermekkori 1-es típusú diabetes mellitus incidenciája Magyarotszágon (1978-1997). Orvosi Hetilap 1999:140;1107-11.

HAGLUND B, RYCKENBERG K, SELINUS O, DAHLGUIST G. Evidence of a relationship between childhood-onset type I diabetes and low groundwater concentration of zinc. Diabetes Care 1996:19;873-6.

HAMMAN RF, GAY EC, GRUICKSHANKS KJ, COOK M, LEZOTTE DC, KLINGENSMITH GJ, CHASE HP. Colorado IDDM Registry. Incidence and validation of IDDM in children ages 0-17 yr. Diabetes Care 1990:13;499-506.

HARDING JE. The nutritional basis of the fetal origins of adult disease. Int J Epidemiol 2001:30;15-23.

HIEMSTRA HS, SCHLOOT NC, VEELEN PA van et al. Cytomegalovirus in autoimmunity: T cell crossreactivity to viral antigen and autoantigen glutamic acid decarboxylase. Proc Natl Acad Sci USA 2001:98;3988-91

HIRASING RA. De incidentie van diabetes mellitus bij 0-19-jarigen in Nederland 1988-1990. Ned Tijdschr Geneeskd 1995:139;1088-92.

HIRASING RA, REESER HM, GROOT RR de, RUWAARD D, BUUREN S van, VERLOOVE-VANHORRICK SP. Trends in hospital admission among children aged 1-19 year with type 1 diabetes in the Netherlands. Diabetes Care 1996:19;431-4.

HIRASING RA, REESER HM, GOOR J van, BRUINING GJ. Nieuw ontdekte diabetes mellitus bij kinderen: wel of niet opnemen. Tijdschr Kindergeneeskunde 1996:65;226-9.

HOOK EB, REGAL RR. Capture-recapture method in epidemiology: Methods and limitations. Epidemiol Rev 1995:17;234-64.

HUNTER I, GREENE SA, MACDONALD TM, MORRIS AD. Prevalence and aetiology of hypothyroidism in the young. Arch Dis Child 2000:83;207-10.

ISOLAURI E, SÜTAS Y, KANKAANPÄÄ P, ARVILOMMI H, SALMINEN S. Probiotics: effects on immunity. Am J Clin Nutr 2001:73(suppl);444S-50S.

KALLIOMÄKI M, SALMINEN S, ARVILOMMI H, KERO P, KOSKINEN P, ISOLAURI E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet 2001:357;1076-9.

KARVONEN M, VIIK-KAJANDER M, MOLLTCHANOVA E, LIBMAN I, LAPORT R, TUOMILEHTO J. Incidence of childhood type 1 diabetes worldwide. Diabetes Care 2000:23;1516-26.

KRAUSE I, BLANK M, SHOENFELD Y. Immunomodulation of experimental autoimmune diseases via oral tolerance. Crit Rev Immunol 2000:20;1-16.

METTEUCCI E, GIAMPIETRO O. Oxidative stress in families of type 1 diabetic patients. Diabetes Care 2000:23;1182-6.

MELONI G, COLOMBO C, LA VECCHIA C, PACIFICO A, TOMASI P, OGANA A, MARINARO AM, MELONI T. High prevalence of lactose absorbers in Northern Sardinian patients with type 1 and type 2 diabetes mellitus. Am J Clin Nutr 2001:73;582-5.

MUNTONI S, COCCO P, ARU G, CUCCA F, MUNTONI S. Nutritional factors and worldwide incidence of childhood diabetes type 1. Am J Clin Nutr 2000:71;1525-9.

REESER HM. Epidemiology of childhood diabetes mellitus in the Netherlands. Thesis, State University Leiden, 1998.

ROOD van JJ, CLAAS F. Both self and non-inherited maternal HLA antigens influence the immune response. Immunol Today 2000:21;269-72.

SCHATZ DA, BINGLEY PJ. Update on major trials for the prevention of type 1 diabetes mellitus: the American Diabetes Prevention Trial (DPT-1) and the European Nicotinamide Diabetes Intervention Trial (ENDIT). J Pediatr Endocrinol Metab 2001:14Suppl 1:619-22.

SHEHADEH H, GELERTNER L, BLAZER S, PERLMAN R, SOLOVACHIK L, ETZIONI A. Importance of insulin content in infant diet: suggestion for a new infant formula. Act Pædiatr 2001:90;93-5.

STATISTICS NETHERLANDS, CENTRAAL BUREAU VOOR DE STATISTIEK (CBS). Population 0-14 years old during 1996-2000. http://www.CBS.nl/en/figures/keyfigures/index.htm

STENE LC, MAGNUS P, LIE RT, SØVIK O, JONER G. Birth weight and childhood onset type 1 diabetes: population based cohort study. BMJ 2001:322;889-92.

VAANDRAGER GJ. De incidentie van insulie-afhankelijke diabetes mellitus bij 0-19 jarigen in Nederland. NIPG-TNO, 1984.

VOS C, REESER HM, HIRASING RA, BRUINING GJ. Confirmation of high incidence of type 1 (insulin dependent) diabetes mellitus in Moroccan children in the Netherlands. Diab Med 1997:14;397-400.

VREUGDENHIL GR. Enteroviruses and type 1 diabetes mellitus: putative pathogenic pathways. Thesis, Catholic University Nijmegen, 2001.

WAAIJ D van der. Role of the intestinal microflora and the immune system of mother mice in the development of a "wasting syndrome" in their congenitally thymusless offspring. March 2001. http://www.ISGNAS.org

A DPSU registration card

89 NSCK MELDINGSKAART

Voor signalering in ***FEBRUARI*** 2000

geen meldingen ☐

		Initialen en geboortedatum gesignaleerde patiënten
1. Coeliakie	☐	....
2. Acute slappe verlamming (inclusief Guillain Barré en bulbair paralyse)	☐	....
3. Diabetes Mellitus	☐	.....
4. Neurale buis-defect(en)	☐	....
5. AIDS/HIV (expositie)	☐	.....
6. Opname i.v.m. Kinkhoest	☐	.....
7. Groep B streptokokkenziekten (0-90 dg)	☐	.....
8. Adrenogenitaal syndroom	☐	....
9. Chronisch Inflammatoire darmziekten	☐	....
10. Neonatale Allo-Immuun ThrombocytoPenie	☐	....

Zie achterzijde voor verdere informatie

De kaart a.u.b. binnen 2 weken na ontvangst terugsturen

Deze kaart heeft betrekking op de signalering in de aan ommezijde aangegeven maand. Wilt u daar ook de nieuwe gevallen van te signaleren aandoeningen aangeven?
Indien u geen van vermelde aandoeningen heeft gesignaleerd kunt u een kruis plaatsen achter 'geen meldingen'
Voor de signalering van de vermelde aandoeningen kunt u de lijst van casusdefinities en zonodig de protocollen raadplegen. Indien u één van de genoemde aandoeningen in deze maand gesignaleerd heeft, plaats a.u.b. een kruisje achter de aandoening met daarachter de initialen en geboortedatum van de patiënt(en). Dit om de verdere activiteiten te vereenvoudigen en dubbelmeldingen te voorkomen. Wilt u de kaart a.u.b. binnen 2 weken ingevuld (dus ook als u niets te melden heeft) in bijgesloten antwoordenveloppe terugsturen.
Of naar:
TNO-PG, t.a.v. R.A. Hirasing, Antwoordnummer 10080, 2300 VB Leiden
Een postzegel is niet nodig.

B DPSU questionnaire

Vragenlijst Insuline Afhankelijk Diabetes Mellitus n.a.v. signalering via het Nederlands Signalerings-Centrum Kindergeneeskunde

Contactpersoon: H.M. Reeser, telefoon 070-3127200

Wij verzoeken u de vragenlijst zo volledig mogelijk in te vullen.
Bij vragen kunt u contact met ons opnemen.
Alvast bedankt voor uw medewerking.

NSCK- code

Naam signalerende kinderarts: .....
Naam ziekenhuis: .....
Gegevens van het kind met insuline-afhankelijke diabetes mellitus
1.Geboortedatum : ----. ----. 19 ----

2.Geslacht: : jongen meisje

3.Huidige woonplaats : ..... Postcode

4.Land van herkomst :

Vader	Moeder
Nederland	Nederland
Ned. Antillen	Ned. Antillen
Suriname	Suriname
Turkije	Turkije
Marokko	Marokko
anders:	anders:

5.Heeft Patiënt altijd in Nederland gewoond? ja neen, patiënt woont sedert----- ----- 19--- in Nederland

6. Heeft het kind borst voeding gehad? ja neen
Zo ja, hoe lang werd uitsluitend borstvoeding gegeven ---- maanden
Na hoeveel maanden werd de borstvoeding geheel gestaakt? ---- maanden

7. Heeft het kind kustvoeding gehad? ja neen
Zo ja,
a. wanneer is daarmee begonnen? ---- ---- 19--
b welke kunstvoeding(en)? .....

8 Heeft het kind in de laatste zes maanden een inenting tegen bof/mazelen/rodehond (BMR) gehad? ja neen
Zo ja, op welke datum? ---- ----- 19—

9. Duur van de verschijnselen voor het stellen van de diagnose: .....dagen

10. Datum van de klinische diagnose: ---- ---- 19--

11. Enkele kenmerken bij de diagnose:

a. Bloed Glucose	.....			
b Ketonurie	ja	neen		onbekend
c pH (bloed)	.....			
d Actueel Bicarbonaat	.....			
e Bewustzijn	normaal	verminderd	comateus	onbekend
f Hydratietoestand		normaal	verminderd	onbekend

12. Datum van de eerste insuline injectie: ---- ----- 19—

13.Werd het kind opgenomen bij het begin van de behandeling: ja neen

Zo ja,

a. Datum van de eerste opname dag: ---- ---- 19--

b. Duur opname: ..... Dagen

14. Heeft patiënte in de afgelopen 12 maanden een infectieziekte doorgemaakt?

neen

ja, in.....(maand invullen)

15. Is patiënt in de afgelopen 12 maanden opgenomen geweest?

neen

ja, en wel voor .....

16. A) Heeft patiënt in de neonatale periode fototherapie gehad vanwege icterus?

neen

ja

zo ja, wat was de oorzaak?.....

B) Is de patiënt ook gewisseld?

neen

ja

17. Is er voor kinderen in uw ziekenhuis een diabetes verpleegkundige beschikbaar?

ja neen

Zo ja, Gaar de diabetesverpleegkundige op huisbezoek? ja neen

---

Gaarne retourneren voor ..... Middels bijgesloten antwoordenvelop of naar

TNO-PG Antwoordnummer 10080, 2300 VB Leiden

C Kolibri questionnaire

13/10/95 14:47 IMMUNOHEMAT BLOODBANK → 31104636811 NR. 483 013

onderzoek type-1 diabetes mellitus zuid-west nederland
Coördinator: Dr. G.J. Brüning, kinderarts, Sophia Kinderziekenhuis, Dr. Molewaterplein 60, Sp-3485, 3015 GJ Rotterdam; tel: 010-463-5779 / 6046; fax: 010-463-6811

Aan: _____

_____

_____

_____

FAX: _____

_____

Geachte collega,

Bij deze bevestigen wij de ontvangst van bloed volgens het protocol 'Type-1 diabetes mellitus in Zuid-west Nederland'.

Naam patiënt: _____ Geslacht: M / V

Patiënt code: KD_____

Geboortedatum: _____ _____ _____

Diagnose datum kinderarts: _____ _____ _____

Datum inzending: _____ _____ _____

Wij ontvingen van U: vooraanmelding/heparine bloed/serum/vragenlijst index patiënt

Wij verzoeken U vriendelijk om eventuele ontbrekende gegevens zo spoedig mogelijk aan ons door te geven.

Eventuele opmerkingen:

_____

_____

_____

Hartelijk dank voor Uw medewerking!

Voor inlichtingen kunt U contact opnemen met ondergetekende.
Met vriendelijke groeten namens het onderzoeksteam,

Dr. B.O. Roep
Afd. Immunohaematologie & Bloedbank
Academisch Ziekenhuis Leiden
Tel.: 071 - 526 3669 / 3600
FAX: 071 - 521 6751

Het 'Onderzoek type-1 diabetes zuid-west nederland' is een samenwerking tussen het Sophia Kinderziekenhuis Rotterdam (afd. Kindergeneeskunde), het Academisch Ziekenhuis Leiden (afd. Immunohaematologie & Bloedbank), en TNO-Preventie en Gezondheid, Leiden. Het onderzoek wordt mede gefinancierd door het Diabetes Fonds Nederland.

Vragenlijst
Index-patient
(door kinderarts in te vullen)

IN IEDER GEVAL DIT EERSTE VEL MEESTUREN MET BLOEDMONSTERS;
dan de overige vragen z.s.m. insturen

Algemene gegevens insturend arts.
Ingestuurd door:
Ziekenhuis :
Te :
tel :
fax :
Basis gegevens:
Naam patiënt Indien bekend: KD nummer
Geb. Datum:
M V KD__-
Datum Diagnose:

De familie van de patiënt is ingelicht over de mogelijk mee te doen aan het onderzoek onder gezonde familieleden.
Ja Nee
De familie wil hier aan meedoen:
Ja Nee De familie denkt hierover nog na
De rest van de vragenlijst gaat hierbij Ja Nee
De rest van deze vragenlijst volgt nog Ja Nee

Deze vragenlijst werdt ingevuld op:

A. ALGEMENE GEGEVENS VAN KIND MET NIEUW ONTDEKT TYPE-1 DIABETES
1. **Naam:** **Kolibri KD Nummer:**
(indien bekend)
2. Geboortedatum: _____-_____-_____ (dd-mm-jj)
3. Datum eerste insuline injectie:_____- _____ -_____(dd-mm-jj)
4. Geslacht: M V
5. Postcode:
6. Land van herkomst:
Vader Moeder
Nederland
Ned. Antillen
Suriname
Turkije
Marokko
anders

7. Heeft dit kind altijd in Nederland gewoond Ja
Nee, sinds ____19_ in Nederland, daarvoor in

8. Heeft het kind in de laatste 6 maanden een inenting gehad
Ja Nee Zo ja op welke datum: _____19

9. Indien JA welke: bof/mazelen/rubella (BMR)
DKTP
BCG
Haemofilus Influ.B vaccinatie (HIB)
andere: (bv i.v.m. tropenreis)

10. Heeft het kind in de afgelopen 12 maanden infectieziekten doorgemaakt?
Ja Nee

11. Welke ziekten?

12. Zijn er andere ziekten of opnames geweest in de afgelopen 12 maanden?
Nee Ja, in verband met

13. Is het kind met andere ziekten of afwijkingen bekend?
Nee Ja

B. SPECIFIEKE GEGEVENS BETREFFENDE DE DIABETES VAN DIT KIND.

14. Datum klinische diagnose: _____- _____-

15. Datum eerste insuline toedienen: _____- _____-

16. Opname: Ja Nee

C. DIAGNOSTIEK.
(waarden van voor start insulinetherapie)

17.De glucose in het bloed was bij binnenkomst: mmol/l

18. Er was bij binnenkomst sprake van gluco- Ja Nee
en/of ketonurie Ja Nee

19. Wat was de pH bij binnenkomst/opname?

20. Zijn er aanwijzingen voor een infectie die nu, naast de diagnose diabetes speelt? Ja Nee

21. Zo ja. Gaarne toelichten

D.FAMILIEGEGEVENS

		IDDM J/N	NIDDM J/N	Andere ziekte	bijzonderheden
22	Moeder van moeder				
23	Vader van moeder				
24	Moeder van vader				
25	Vader van vader				
26	00 Moeder				
27	01 Vader				
28	02 sib-1 M/V				
29	03 sib 2 M/V				
30	04 sib 3 M/V				
31	05 sib 4 M/V				
32					
33					
34					
35					

S.V.P. Bij index patiënt (=nieuwe diabetes patiënt) het nummer omcirkelen

36. Familieleden (ooms, tantes, etc.) aan moeders kant met diabetes (zowel insuline afhankelijk als ouderdoms diabetes)?

Ja Nee

Graag specificeren:

37. Familieleden (ooms, tantes etc.) aan vaders kant met diabetes (zowel insuline afhankelijke als ouderdoms diabetes)?

Ja Nee

Graag specificeren:

38. Overige opmerking die U van belang acht in het kader van de diagnose diabetes mellitus

D DDA questionnaire

FORMULIER A Voorbeeld voor Bassie Springveld; zo invullen

initialen	man=m vrouw=v	geboortedatum			datum 1e insuline-injectie			woonplaats op moment van 1e insuline-injectie	postcode op moment van 1e insuline-injectie	land van herkomst eigen moeder	land van herkomst eigen vader	eventuele opmerkingen
		dag	mnd	jaar	dag	mnd	jaar					
B.S.	*M*	*12*	*10*	*86*	*6*	*5*	*99*	*Geleen*	*6163 AH*	X Nederland O Ned. Antillen O Marokko O Suriname O Turkije O anders	X Nederland O Ned.. Antillen O Marokko O Suriname O Turkije O anders	*Geen*

Hieronder gegevens invullen door hen die lid werden in 1998, 1999 en 2000

initialen	man=m vrouw=v	geboortedatum			datum 1e insuline-injectie			woonplaats op moment van 1e insuline-injectie	postcode op moment van 1e insuline-injectie	land van herkomst eigen moeder	land van herkomst eigen vader	eventuele opmerkingen
		dag	mnd	jaar	dag	mnd	jaar					
										O Nederland O Ned.. Antillen O Marokko O Suriname O Turkije O anders	O Nederland O Ned.. Antillen O Marokko O Suriname O Turkije O anders	

was u ten tijde van de 1e insuline-injectie onder behandeling van:

kinderarts	zo ja, naam kinderarts:	plaats:
internist	zo ja, naam internist:	plaats:
niet bij kinderarts, ook niet bij internist	zo ja, bij wie onder behandeling naam: beroep:	plaats:

Zou u dit formulier **binnen 1 week** willen opsturen in bijgevoegde antwoordenveloppe? Een postzegel is **niet** nodig.
Bij kwijtraken: in enveloppe zonder postzegel op sturen naar: Dr. J.P. van Wouwe, TNO-PG, Antwoordnummer 10080, 2300 VB LEIDEN.
Nogmaals bedankt voor uw medewerking.

Formulier B

Formulier voor aanmelding voor eventueel vervolg onderzoek

Let op: invullen van dit formulier verplicht u niet tot deelname aan vervolg onderzoek. Het maakt allen uitnodiging daarvoor mogelijk.

Ondergetekende.
.....

Voorletters naam
Ouder/verzoger van:
.....

voornaam naam geboortedatum
.....

adres
.....

postcode woonplaats

geven hierbij toestemming voor het toezenden van vragen lijsten over factoren die bijdragen aan het ontstaan, de beleving en het verloop van diabetes bij jeugdigen. Na ontvangst van de vragenlijsten zullen ondergetekende(n) beslissen of zij ook daadwerkelijk aan het vervolgonderzoek zullen deelnemen.
Plaats..... Datum.....

Indien kind ouder dan 12 jaar is:

Handtekening ouder / verzorger Handtekening kind
....