European Journal of Endocrinology (2007) **157** 175–180 ISSN 0804-4643

CLINICAL STUDY

Type 2 diabetes in children in the Netherlands: the need for diagnostic protocols

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Abstract

Objective: The worldwide trend towards obesity in childhood is also observed in the Netherlands and one of the consequences may be type 2 diabetes. In this study, we assessed the number of children with type 2 diabetes, diagnosed by paediatricians, in the Netherlands.

Methods: In 2003 and 2004 the Dutch Paediatric Surveillance Unit, a nationwide paediatric register, was used to assess new cases of diabetes mellitus. Data on socio-demographic and clinical characteristics were collected by means of a questionnaire. A second questionnaire was sent to the reporting paediatrician if the diagnosis was inconclusive or if the diagnosis was type 1 diabetes in combination with overweight or obesity, according to international criteria.

Results: During the 24 months of registration, the paediatricians reported 1142 new cases of diabetes, 943 of which were eligible for analysis. Initially, 14 patients (1.5%) were reported with type 2 diabetes. Only seven of these patients were classified as type 2 diabetes according to the ADA criteria, as information on C-peptides or antibodies was often missing. Based on clinical characteristics, the other seven patients were very likely to have type 2 diabetes. After the second questionnaire, six more patients met the ADA criteria and two were very likely to have type 2 diabetes. Most of the patients were female (95%), 14% were of Turkish and 18% of Moroccan origin.

Conclusion: This study shows a discrepancy between the number of patients with type 2 diabetes diagnosed by paediatricians in daily practice and diagnosed according to the ADA criteria. Moreover, a considerable amount of reported patients were misclassified. Finally, 2.4% patients were classified as (very likely) type 2 diabetes. The development of programmes and protocols for prevention, diagnosis and classification applicable in daily practice is warranted.

European Journal of Endocrinology **157** 175–180

Introduction

Over the past two decades, the prevalence of overweight and obesity in children has increased rapidly worldwide (1). In the period between 1980 and 1997, overweight among 5- to 11-year-old boys increased from 3–5% to 7–12% in the Netherlands, and obesity increased from 0.1–0.3% to 0.8–1.6%. Comparable trends were found in girls (2, 3). The increases in the prevalence of overweight and obesity are alarming, because childhood obesity is associated with a wide range of serious medical complications, such as the metabolic syndrome, type 2 diabetes and cardiovascular disease (4, 5). In the United States, type 2 diabetes now accounts for a considerable proportion of newly diagnosed diabetes in children (5).

Only few data are available on type 2 diabetes mellitus in paediatric patients in Europe. The incidence of type 2 diabetes among children in the Netherlands is unknown. This information is important for public health policy and also for health professionals for the early detection and treatment of type 2 diabetes in obese children. Delayed diagnosis, poor glucose control during adolescence and a long duration of diabetes may all predispose to the early onset of complications in adulthood.

Considering the severity of the problem, we looked for an existing registration system that could be used to systematically collect information on children and adolescents with type 2 diabetes. We considered the Dutch Paediatric Surveillance Unit (DPSU) registration system to be the most suitable to study type 2 diabetes among children and adolescents. Since it can be difficult

DOI: 10.1530/EJE-06-0754
Online version via www.eje-online.org

to distinguish type 2 diabetes from other forms of diabetes, both type 1 and type 2 diabetes were registered in order to detect misclassification by the paediatrician. The research question we addressed was: How often is type 2 diabetes diagnosed among children by paediatricians?

Methods

In the period from January 2003 to December 2004, cases of new onset type 1 and type 2 diabetes among children and adolescents in the Netherlands, diagnosed by paediatricians, were registered prospectively by the DPSU. This Unit was founded in 1992 under the auspices of the Dutch Society for Paediatrics. The aim of the Unit is to monitor the incidence of rare or new diseases in youth aged 0–18 years. Moreover, it also aims to stimulate research in the field of the aetiology, diagnostics, treatment and prevention of these new diseases. The Unit requested all paediatricians working in general hospitals to report all newly diagnosed cases of type 1 and type 2 diabetes monthly. Therefore, all paediatricians received a DPSU card on a monthly basis. They were asked to return this card reporting all newly diagnosed cases of diabetes or marking the 'nothing to report' box. Each of the eight University Medical Centres nominated a specific contact person who was responsible for reporting. There are no private paediatric clinics in the Netherlands. In 2003 and 2004 97 and 95% respectively of the paediatricians who had been contacted returned the monthly card to the DPSU. The researchers sent a short questionnaire to all paediatricians who reported a case to the DPSU. The purpose of this questionnaire was to collect data on type of diabetes, ethnicity, blood pressure, weight and height of the patient, presenting symptoms (polyuria, polydipsia) before the diagnosis of diabetes, laboratory results (glucose, ketones), autoantibodies (islet cell antibodies and/or GAD65 and/or IA-2), treatment (insulin, oral medication) and family history of diabetes.

A second questionnaire was sent if the diagnosis was inconclusive or it was type 1 diabetes and the patient was overweight or obese, according to international age- and gender-specific criteria (6). The second questionnaire focussed, among other things, on the course of the disease and the treatment modality.

At first we described the number of children with type 2 diabetes diagnosed and reported by paediatricians that also met the ADA criteria. However, in many patients, information on C-peptides or antibodies was missing. Therefore, it was decided to study also which patients could be considered as very likely having type 2 diabetes based on available information on body mass index, autoantibodies, medication and clinical parameters.

The baseline characteristics of patients who were diagnosed with type 1 and type 2 diabetes were compared with χ^2-tests, *t*-tests and Fisher's exact tests.

Results

During the 24-month registration period, a total of 1142 children with a new onset of diabetes mellitus were reported to the DPSU (Fig. 1). The response rate for the first questionnaire concerning 1062 valid cases (502 diagnosed in 2003 and 560 in 2004) was 88.8%, so 943 patients were eligible for analysis.

Initially, 838 patients (88.9%) were registered with type 1 diabetes, 14 patients (1.5%) with type 2 diabetes, 26 (2.8%) with some other type of diabetes such as maturity onset diabetes of the young, cystic fibrosis-related diabetes and mitochondrial diabetes and 65 (6.9%) with an unknown type of diabetes.

After the first questionnaire, 7 of 14 patients reported with type 2 diabetes were diagnosed as type 2 diabetics according to the American Diabetes Association (ADA) criteria. In the remaining seven patients, information especially on C-peptides was missing. These seven patients, however, could be diagnosed as very likely type 2 diabetes based on their characteristics: they all were obese or overweight, five patients who had negative autoantibodies were treated with oral medication, and had no ketonuria. The other two also met these characteristics except that one patient missed information on ketonuria and another one on autoantibodies (Table 1).

A second questionnaire was sent to the paediatricians of 65 patients for whom the diagnosis was inconclusive and to the paediatricians of 91 patients with type 1 diabetes who were overweight or obese, according to international criteria (6).

Based on this second questionnaire, six more patients initially reported as patients with type 1 diabetes or an inconclusive diagnosis could be classified as type 2 diabetes according to ADA criteria. Another two patients were diagnosed as very likely type 2 diabetes based on their characteristics. Both patients had overweight, negative antibodies and were treated with insulin.

Of the 65 patients in which the paediatrician did not initially establish a diagnosis, only in 23 patients did the final diagnosis remain inconclusive (see Fig. 1).

Finally, 870 patients were diagnosed with type 1 diabetes, 13 (1.4%) with type 2 diabetes according to the ADA criteria and 9 (1.0%) with very likely type 2 diabetes. Clinical characteristics of the 22 patients reported with type 2 diabetes are shown in Table 1.

All 14 patients who were classified by the paediatrician as type 2 diabetics after the first questionnaire were girls aged 12 to 17 years. The second group initially defined as type 1 diabetes or an inconclusive

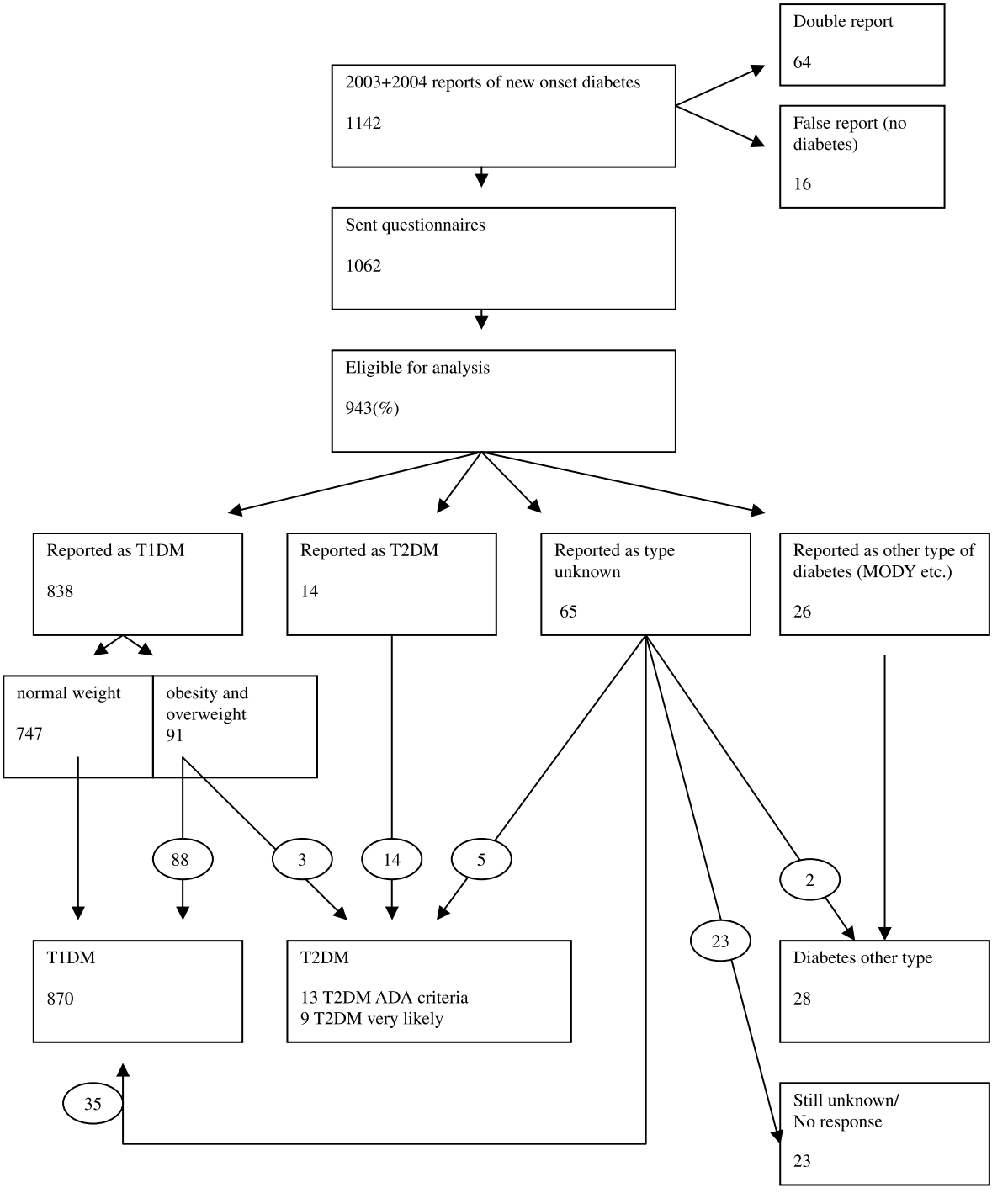

Figure 1 Patient flow chart.

diagnosis consisted of seven girls and one boy, within an age range of 9–15 years.

Finally, of the 13 patients (12 girls and 1 boy) with type 2 diabetes according to the ADA criteria, 9 were obese and 4 were overweight. Two of these patients were of Moroccan and two were of Turkish origin. Of the 9 patients with very likely type 2 diabetes (9 girls), 6 were obese and 3 were overweight. Of these patients, 1 was Turkish and 2 were Moroccan.

In the group of patients classified as type 1 diabetes, antibody analysis was performed in 655 (75.9%) patients. The results were available for 469 (53.9%) patients. Of these patients, 306 had positive antibodies

Table 1 Characteristics of the 22 patients with type 2 diabetes according to ADA guidelines and very likely diabetes.

Sex	Age	Country father	ADA	Over weight	Obesity	Polyuria	Polydipsia	Ketonuria	C-peptide	Antibodies	Therapy
First questionnaire											
F	16	N	−	−	+	−	−	−	np	np	o
F	15	N	+	−	+	+	+	−	↑	−	o
F	17	T	−	−	+	−	−	−	np	−	o
F	17	N	+	−	+	−	+	−	↑	−	o
F	17	N	−	+	−	+	+	na	np	−	o
F	13	M	−	−	+	+	+	−	np	−	o
F	19	N	+	−	+	+	+	−	↑	−	o
F	12	N	+	−	+	+	+	+	↑	−	i
F	12	T	+	+	−	−	−	−	↑	−	o
F	12	M	+	−	+	+	+	−	↑	−	i
F	14	N	−	−	+	−	−	−	np	−	o
F	16	N	−	−	+	+	+	−	np	−	o
F	17	O	+	−	+	−	−	−	↑	−	i
F	13	N	−	−	+	+	+	−	np	−	o
Second questionnaire											
F	9	N	+	+	−	+	na	−	↑	−	o
F	11	O	−	+	−	+	+	+	np	−	i
M	9	N	+	+	_	+	+	+	↑	−	i
F	10	N	+	−	+	+	+	+	↑	np	o
F	13	SA	+	−	+	−	−	−	↑	np	o
F	14	T	+	−	+	−	−	−	↑	−	o
F	12	M	+	+	−	+	+	+	↑	−	i
F	15	M	−	+	−	−	−	−	np	−	i

−, negative; +, positive; na, not available; np, not performed. Sex: F, female; M, male. Father's country of origin: N, the Netherlands; T, Turkey; M, Morocco; SA, South America; O, other. ADA: +, type 2 diabetes following ADA guidelines; −, very likely type 2 diabetes, overweight and obesity according to Cole criteria. C-peptide: ↑, increased C-peptide levels. Therapy: o, oral medication; i, insulin.

(65%), 146 had negative antibodies (31.1%) and 18 had dubious antibodies (3.8%; Table 2). C-peptide levels had been assessed in none of the patients reported with type 1 diabetes.

In the group classified as having type 2 diabetes, antibody analysis was performed in 19 of 22 patients. The result of antibody analysis was negative in all of them. C-peptide levels had been assessed in only 13 of these 22 patients and they were elevated in all of them.

Patients with type 2 diabetes were older, more often female and more overweight or obese than patients with type 1 diabetes ($P<0.001$). Furthermore, ketonuria, polydipsia and polyuria were less often present in patients with type 2 diabetes. ($P<0.001$; Table 2).

Discussion

This is a descriptive study to assess the number of children and adolescents with T2DM, diagnosed by paediatricians, from the Netherlands, during 2 years (2003–2004). A nationwide paediatric register was used to perform this population-based study and it describes clinical practice in establishing the diagnosis of diabetes, especially type 2 diabetes.

Our study of type 2 diabetes is relevant in the wake of the expanding epidemic of obesity in Western countries; only a few years ago type 2 diabetes was never diagnosed in the Netherlands. However, the results of studies in Europe have emphasized that the prevalence of type 2 diabetes is rising (7–10). Our study is the first national population-based study to show that type 2 diabetes is now prevalent among children in the Netherlands: 1.4% of children with new onset diabetes as diagnosed by the paediatrician have type 2 diabetes according to the ADA criteria, whereas the diagnosis is very likely in another 1.0%. However, it was not the objective of this study to calculate incidence rates of type 2 diabetes among children in the Netherlands. Moreover, the incidence of type 2 diabetes cannot be reliably calculated from this

Table 2 Patient characteristics and findings on presentation.

	Type 1 diabetes	Type 2 diabetes
N	870	22
Age years (±S.D.)†	9.1 (4.1)	13.8 (2.8)
% Female†	46	96
BMI SDS (±S.D.)†	−0.9 (1.5)	2.3 (0.7)
Father's country of origin†		
Netherlands (%)	684 (82%)	12 (55%)
Turkey (%)	20 (2%)	3 (14%)
Morocco (%)	60 (7%)	4 (18%)
Other countries (%)	70 (8%)	3 (14%)
Polyuria (%)†	834 (97%)	13 (59%)
Polydipsia (%)†	826 (97%)	62 (13%)
Ketonuria (%)†	585 (75%)	5 (24%)
Autoantibodies (% positive)†	306 (65%)	0
Family history type 2 diabetes (%)	486 (58%)	15 (79%)

BMI, body mass index, †$P<0.001$.

registration. A true incidence rate can only be determined in a complete assessment study.

Nearly 40% of the patients in our study with type 2 diabetes were initially registered as type 1 diabetes or as inconclusive. Misclassification by paediatricians has also been mentioned in other studies. In a study of 661 children in Florida, 3% of the children who were diagnosed with type 1 diabetes were reclassified as having type 2 diabetes, and 8% of those initially diagnosed with type 2 diabetes were reclassified as having type 1 diabetes (11). Another problem in the initial diagnosis is that patients with type 1 diabetes are becoming more obese (12). These difficulties in the establishment of the diagnosis underline the need for a strict diagnostic work-up. Diagnostic flowcharts and protocols do exist (4, 13), but are obviously rarely used by paediatricians. Although antibody analysis can be negative in patients with type 1 diabetes and positive in patients with type 2 diabetes, it should be performed for all patients with new onset diabetes to support the diagnosis of type 1 or type 2 diabetes. In this respect, the fact that antibody analysis was only performed for 75% of the patients in our study with type 1 diabetes and that the results were known for 54% is worrying.

A second measurement that should be taken before a diagnosis of type 2 diabetes is confirmed is C-peptide. This can only be used to support the diagnosis, because there is considerable overlap in C-peptide measurements at the onset of diabetes and during the first year in both type 1 and type 2 diabetes. Elevated levels of C-peptide indicate type 2 diabetes, but normal or suppressed levels do not.

The clinical characteristics of the patients in this study who were diagnosed with type 2 diabetes indicate that the diagnosis of type 1 diabetes is highly unlikely. All patients who were diagnosed with type 2 diabetes were overweight or obese and the majority were treated with oral antidiabetic agents and also had negative antibody analysis.

Type 2 diabetes was diagnosed almost exclusively in girls, especially after the first questionnaire. This is higher than the female/male ratios ranging from 1.3 to 3 found in other studies (1) and may be due to small group size.

Type 2 diabetes was more often diagnosed in Turkish and Moroccan children. Of the children with a diagnosis of type 2 diabetes, four (18%) were Moroccan and three (14%) were Turkish. This is a higher percentage than expected from the distribution of ethnicity in the general population, which is 3.1 and 3.6% respectively (14). These ethnic groups are more at risk for the development of obesity (15) and may be more at risk for type 2 diabetes.

The number of children and adolescents in our study with type 2 diabetes is minimal. Some obese adolescents may have been diagnosed by specialists in internal medicine instead of paediatricians, because of their posture and adult appearance. It is also unclear how many children and adolescents in the general population are undiagnosed or diagnosed and treated by general practitioners. Finally, 23 patients were not assigned a definite diagnosis. The fact that the type of diabetes remained unknown in 23 patients reflects the problems encountered in daily practice as well as the need to work in accordance with diagnostic protocols.

The percentage of children in the Netherlands with new onset diabetes, diagnosed with type 2 diabetes by paediatricians, is considerable. The fact that the paediatricians are not using protocols to establish an accurate diagnosis is worrying. The numbers may, therefore, be much higher since misclassification or an inconclusive diagnosis by a paediatrician occurs in a substantial number of patients with new onset diabetes mellitus. This emphasizes the need for clear uniform protocols for the diagnosis and treatment of patients with type 2 diabetes.

This study shows that current clinical practice among paediatricians is insufficient for proper classification. Although 100% correct classification is unlikely, the use of strict guidelines and recommendations applicable within daily practice could improve the number of correct classifications dramatically. This is very important with respect to the rapid increase in the prevalence of obesity in children and adolescents that is accompanied with a rapid increase in the prevalence of type 2 diabetes.

From the perspective of the public health policy, and considering the ever-increasing prevalence of obesity, it seems necessary to monitor obese children and adolescents and to study trends in incidence, prevalence, prognosis and related complications and quality of life.

However, even more important than monitoring children and adolescents with type 2 diabetes is the prevention of obesity, starting at an early age.

Acknowledgements

We wish to thank the paediatricians who reported their patients and Ine Cox for all the tedious work that she did for this study.

References

1 Fagot-Campagna A, Saaddine JB, Flegal KM & Beckles GL. Diabetes, impaired fasting glucose, and elevated HbA1c in US adolescents: the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2001 **24** 834–837.

2 Fredriks AM, van Buuren S, Fekkes M, Verloove-Vanhorick SP & Wit JM Growth diagrams. Fourth Dutch Nation-wide survey 1997. *Thesis* 2004. 91–105.

3 Hirasing RA, Fredriks AM, van Buuren S, Verloove-Vanhorick SP & Wit JM. Increased prevalence of overweight and obesity in Dutch

children, and the detection of overweight and obesity using international criteria and new reference diagrams. *Nederlands Tijdschrift Voor Geneeskunde* 2001 **145** 1303–1308.
4 American Diabetes Association. Type 2 diabetes in children and adolescents. *Diabetes Care* 2000 **23** 381–389.
5 Hannon TS, Rao G & Arslanian SA. Childhood obesity and type 2 diabetes mellitus. *Pediatrics* 2005 **116** 473–480.
6 Cole TJ, Bellizzi MC, Flegal KM & Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000 **320** 1240–1243.
7 Ehtisham S, Hattersley AT, Dunger DB & Barrett TG. First UK survey of paediatric type 2 diabetes and MODY. *Archives of Disease in Childhood* 2004 **89** 526–529.
8 Ortega-Rodriguez E, Levy-Marchal C, Tubiana N, Czernichow P & Polak M. Emergence of type 2 diabetes in an hospital based cohort of children with diabetes mellitus. *Diabetes and Metabolism* 2001 **27** 574–578.
9 Rami B, Schober E, Nachbauer E & Waldhor T. Type 2 diabetes mellitus is rare but not absent in children under 15 years of age in Austria. *European Journal of Pediatrics* 2003 **162** 850–852.
10 Schober E, Holl RW, Grabert M, Thon A, Rami B, Kapellen T, Seewi O & Reinehr T. Diabetes mellitus type 2 in childhood and adolescence in Germany and parts of Austria. *European Journal of Pediatrics* 2005 **164** 705–707.
11 Macaluso CJ, Bauer UE, Deeb LC, Malone JI, Chaudhari M, Silverstein J, Eidson M, Goldberg RB, Gaughan-Bailey B, Brooks RG & Rosenbloom AL. Type 2 diabetes mellitus among Florida children and adolescents, 1994 through 1998. *Public Health Reports* 2002 **117** 373–379.
12 Strauss RS & Pollack HA. Epidemic increase in childhood overweight, 1986–1998. *JAMA* 2001 **286** 2845–2848.
13 Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004 **27** S5–S10.
14 Central Office of Statistics, The Netherlands, www.cbs.nl; www.statline.nl
15 Fredriks AM, van Buuren S, Sing RA, Wit JM & Verloove-Vanhorick SP. Alarming prevalences of overweight and obesity for children of Turkish, Moroccan and Dutch origin in the Netherlands according to international standards. *Acta Paediatrica* 2005 **94** 496–498.

Received 19 December 2006
Accepted 7 May 2007