Rising Incidence of Type 2 Diabetes in Children in the U.K.

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OBJECTIVE — To estimate the incidence of type 2 diabetes in children <17 years of age and to investigate the relationship of diabetes with increasing childhood obesity in the U.K. and the Republic of Ireland (ROI).

RESEARCH DESIGN AND METHODS — Active monthly reporting of cases by consultant pediatricians occurred through the framework of the British Pediatric Surveillance Unit, with additional reports from specialist diabetes nurses. All children <17 years of age and diagnosed by their clinician as having non–type 1 diabetes from 1 October 2004 to 31 October 2005 were included.

RESULTS — A total of 168 confirmed cases of non–type 1 diabetes were reported, resulting in a national incidence (excluding the ROI) of $1.3 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$. Of these, 40% were diagnosed with type 2 diabetes giving a minimum incidence of $0.53 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$. Children of ethnic minorities were greatly overrepresented, with those of black and South-Asian origin (England data only) having an incidence of 3.9 and $1.25 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$, respectively, compared with $0.35 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$ in those defined as white. Of those diagnosed with type 2 diabetes, 95% were overweight and 83% obese according to International Obesity Task Force guidelines. Eighty-four percent had a family history of type 2 diabetes.

CONCLUSIONS — Type 2 diabetes is still less common than type 1 diabetes in U.K. children. However, compared with previous prevalence data, the frequency of type 2 diabetes appears to be increasing. Incidence among ethnic minorities is far higher than in whites, as previously described in the U.S. Increased adiposity and family history of type 2 diabetes were strongly associated with the diagnosis of type 2 diabetes in U.K. children.

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The growing prevalence of childhood obesity in the U.K. (1,2) undoubtedly has implications for our children's health. Predictions from the U.S. imply that obesity-driven type 2 diabetes might become the most common form of newly diagnosed diabetes in adolescent youth within 10 years (3). Evidence now exists suggesting a global spread of type 2 diabetes in children, although incidence data are uncommon (4). Various centers in the U.S. have recorded dramatic increases in the number of children diagnosed with type 2 diabetes. A 10-fold increase was reported by a center in New York from 1990 to 2000, with 50% of all new cases having type 2 diabetes (5), and similar increases have been reported elsewhere (6). In Japan, researchers have documented a rise in annual incidence from 1.73/100,000 to 2.76/100,000 over 20 years (7), while evidence is emerging of an increase in urban South-Asian children (8). Data from Europe are scarce (9); a population-based study in Austria established an incidence of 0.25/100.000 children (10), while a report from France indicated relatively low but increasing numbers of children presenting with type 2 diabetes (11). In the U.K., Ehtisham et al. (12) estimated a crude prevalence of type 2 diabetes in children aged under 16 years of 0.21/100,000, while a recent report reviewing first hospital admissions with a diagnosis of type 2 diabetes in patients <18 years of age indicated a significant rise between 1996–1997 and 2003–2004 (13).

The emergence of type 2 diabetes in adolescents has important implications for both the health of the individual and health service resources. Treatment compliance (14) and psychological health (15) are often poor in childhood type 2 diabetes. Various studies imply an accelerated risk of nephropathy (16,17) and retinopathy (18) compared with young people with type 1 diabetes, while recent data indicate early signs of cardiovascular disease in youth with type 2 diabetes (19). The only currently available longitudinal data give cause for concern—of 79 children recontacted up to 15 years after the diagnosis of type 2 diabetes, 9% had died and 6% were on dialysis (20).

The growing number of anecdotal reports of increasing type 2 diabetes in U.K. children and a need to establish clinical guidelines and frameworks for their treatment prompted us to initiate a prospective, population-based, surveillance study to establish baseline incidence rates for non–type 1 diabetes and, more specifically, type 2 diabetes in childhood.

RESEARCH DESIGN AND METHODS

— A prospective monthly surveillance of 2,665 consultant pediatricians in the U.K. and the Republic of Ireland (ROI) through the British Pediatric Surveillance Unit (BPSU) of the Royal College of Pediatrics and Child Health was undertaken to identify cases of non–type 1 diabetes in 0- to 16-year-old individuals. The study ran from October 2004 until October 2005 (inclusive). The study received ethical approval from the South West Multi Research Ethics Committee (04/MREC06/39) and was also given approval not to seek patient or pa-

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Abbreviations: BPSU, British Pediatric Surveillance Unit; HNF, hepatocyte nuclear factor; ICA, islet cell antibody; MODY, maturity-onset diabetes of the young; ROI, Republic of Ireland.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

rental consent by the Patient Information Advisory Group [PIAG/BPSU2-10(b)/2005].

A parallel reporting system was set up with diabetes specialist nurses to identify adolescents directly referred to adult services. From a list of diabetes specialist nurses provided by Diabetes UK, an individual was identified and invited to participate from each acute hospital. The 157 nurses who agreed were sent reporting cards every 2 months throughout the study.

Clinicians (pediatricians and nurses) were asked to report any new case of non–type 1 diabetes either suspected or confirmed in the previous month. Cases of non–type 1 diabetes were reported as *1*) type 2 diabetes with evidence of insulin resistance (e.g., acanthosis nigricans, increased fasting insulin, or increased C-peptide), *2*) maturity-onset diabetes of the young (MODY; characterized by known MODY gene mutation), *3*) diabetes as part of a recognized syndrome, *4*) diabetes as part of a suspected or unrecognized syndrome, or *5*) diabetes secondary to another condition (e.g., cystic fibrosis).

With the rising overall prevalence of childhood obesity, children presenting with type 1 or type 2 diabetes may be obese; therefore, obesity itself is not a useful discriminatory marker. Additionally, monogenic forms of diabetes such as MODY have clinical overlap with type 2 diabetes. Consequently, we planned a survey of non–type 1 diabetic cases, using a broad definition, to maximize the capture of type 2 diabetic cases. We excluded obesity from our notification criteria in order to analyze the anthropometric characteristics of the survey children and because obesity itself is a poor discriminator, since children with type 1 diabetes relatively frequently have excess adiposity as general prevalence levels of obesity increase (21). Because of the difficulties of distinguishing type 1 diabetes from non–type 1 diabetes, reports of cases previously diagnosed as having diabetes but newly recognized as atypical for type 1 diabetes were sought (i.e., children initially diagnosed with type 1 diabetes but not presenting characteristics of classical "insulin-dependent" diabetes, e.g., having diabetes but with low or no insulin requirement, excellent control without regular monitoring, few hyperglycemic episodes, absence of ketonuria, and being out of the honeymoon period).

Clinicians reporting a case of non–type 1 diabetes were sent a questionnaire to collect the physician diagnosis, basic demographic details, presenting symptoms, confirmatory diagnostic tests, date of diagnosis, height and weight at diagnosis, and family history of non–type 1 diabetes. Duplicate case reports were identified using hospital number and month and year of birth. When duplicates were identified, data from both questionnaires were collated and recorded. Clinicians not returning the questionnaire within 1 month were reminded by letter and then phone call, with a final reminder letter sent at the end of the study period. To maximize ascertainment, at the end of the reporting period all clinicians reporting cases were sent a list of cases they had notified to confirm that all eligible individuals had been identified.

Completed clinical questionnaires were scrutinized to confirm that the cases met study criteria (case of non–type 1 diabetes diagnosed before the 17th birthday between 1 October 2004 and 31 October 2005) and fulfilled American Diabetes Association criteria for diabetes diagnosis (22). The physician diagnoses were reviewed by the study clinicians (J.P.H.S. and T.G.B.) in light of the information provided on the questionnaire and were reclassified as necessary according to the following case definitions. *1*) Definite type 2 diabetes: clinical questionnaire confirmed the presence of raised insulin (>132 pmol/l or equivalent) or C-peptide levels (>600 pmol/l) and/or the absence of autoimmune antibodies found in type 1 diabetes. *2*) MODY: case reported as MODY with a confirmed gene mutation. *3*) Secondary diabetes: diabetes secondary to another condition. *4*) Syndromic diabetes: extrapancreatic clinical features such as retinal dystrophy or sensorineural deafness that suggest a syndrome such as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). *5*) Unclassified: insufficient clinical information available to classify as any of above. *6*) Type 1 diabetes: positive GAD antibodies or high titers of islet cell antibodies (ICAs).

Pediatricians reporting a confirmed case of non–type 1 diabetes were sent a follow-up questionnaire 1 year after the initial case report, in order to clarify diabetes status and insulin/C-peptide and autoimmunity status. Incidence rates were calculated using population denominators available from the Office of National Statistics.

Table 1—*Classification of reported non–type 1 diabetes cases*

	n (%)
Type 2 diabetes	67 (40)
MODY	17 (10)
Secondary diabetes	37 (22)
Recognized syndrome	13 (8)
Unclassified	34 (20)

RESULTS — A total of 363 cases were reported over the 13 months of study; 250 (69%) through the BPSU and 113 (31%) by diabetes specialist nurses. The mean monthly return over the study period was 93% for BPSU cards and 91% for nurse cards.

Completed clinical questionnaires were received for 94% of reported cases (341 of 363). We excluded 173 (48%) reports because they were duplicates or they included children who were >17 years of age at diagnosis, who were diagnosed outside the study period, or whose diagnosis was not non–type 1 diabetes.

After careful review of questionnaires, 168 cases were confirmed as meeting study criteria for non–type 1 diabetes; 126 (75%) were reported by pediatricians and 42 (25%) by nurses. Of the 42 cases reported by nurses, 39 were cared for by a pediatrician, 20 of whom were also reported by the pediatrician, whereas 3 were only being cared for by an adult endocrinologist/diabetologist. The 19 cases reported solely by a nurse but under the care of a pediatrician may reflect a degree of underreporting by pediatricians. However, in most cases, it probably reflects a degree of negative independence of pediatrician and nurse reporting in that one professional is aware of another's report and does not duplicate it. This process was well documented in a previous diabetes survey through the BPSU (23).

All cases of non–type 1 diabetes

The 168 cases of physician-diagnosed non–type 1 diabetes included 67 cases of type 2 diabetes, 17 MODY, 37 secondary, and 18 recognized or unrecognized syndrome (Table 1). There were 34 cases of non–type 1 diabetes that could not be classified because they did not satisfy our criteria for type 2 diabetes and did not fit any other non–type 1 diabetes category.

Of the 168 non–type 1 diabetic cases, 93 were girls and 75 boys (ratio 1.24:1) and the mean age at diagnosis was 12.3 years for girls and 12.7 years for boys (1.2 months to 16.8 years).

In 22% of cases (37 of 168), the child was originally diagnosed as having type 1 diabetes but the clinical course prompted a diagnostic revision. Fourteen cases were revised from type 1 to type 2 diabetes, 8 to MODY, 5 to syndromic diabetes, and 1 to secondary diabetes. Nine cases were revised to an unclassified category of diabetes.

Type 2 diabetes

There were 67 cases of type 2 diabetes, representing 40% (67 of 168) of all non–type 1 cases reported. Fifty-seven percent of cases (38 of 67) were girls, and the mean age at diagnosis was 13.3 ± 1.7 years for girls and 14.1 ± 2.0 years for boys (range 8.3–16.8). Fifty-seven percent of cases were classified as white and 43% as an ethnic minority, predominantly South Asian (35%) and black/black British (45%).

Thirty eight of 67 (57%) cases of type 2 diabetes had acanthosis nigricans, most commonly in the neck and axillae. This was present in only 42% of whites compared with 76% of those classified as black/South Asian or as mixed race (continuity-corrected χ^2 test, $P = 0.012$).

Of the 67 type 2 diabetic cases, 45 had measures of insulin and/or C-peptide levels; raised C-peptide levels (>600 pmol/l) were reported in 12 cases, raised insulin levels (>132 pmol/l) in 15 cases, and both raised insulin and C-peptide levels in 18 cases.

Antibody testing was performed in 79% of type 2 diabetic cases (53 of 67). Antibodies tested included GAD-65 (35 tests; all negative), ICAs (37 tests; 36 negative and 1 weakly positive), and anti-insulin autoantibodies (7 tests; all negative). The one case testing weakly positive for ICAs was negative for GAD-65, suggesting continued type 2 diabetes classification.

In those cases for whom details were recorded (39 of 67), 28% had ketosis at diagnosis, while 7% (5 of 67) of all type 2 diabetic cases were reported as presenting with ketoacidosis. Seven female patients with type 2 diabetes (18% of girls) had additional biochemical evidence of polycystic ovarian syndrome.

BMI z-scores or SD scores at diagnosis were calculated from weight and height. Overweight and obesity were defined as ≥1.30 and ≥2.37, respectively, for boys and ≥1.19 and ≥2.25 for girls (24). Ninety-five percent of children were overweight and 83% obese according to the International Obesity Task Force guidelines. The mean BMI SD score, estimated using the 1990 U.K. growth standards (25), was 3.04 for girls and 2.45 for boys.

In 84% (56 of 67) of cases, a first- or second-degree family history of diabetes was present (71% in first-degree relatives).

Secondary diabetes

A total of 37 children (21 girls and 16 boys) had diabetes secondary to another condition. The most common disease association was cystic fibrosis (57%), followed by iatrogenic causes such as steroid-induced diabetes after renal or bone marrow transplantation. All children with secondary diabetes were white, with two exceptions (one South Asian and one mixed race).

MODY

There were 17 MODY cases, 9 (53%) of whom were female. Mean age at presentation was 11.9 ± 3.65 for girls and 12.5 ± 4.4 for boys. The 17 confirmed molecular diagnosis cases included 7 glucokinase, 6 hepatocyte nuclear factor (HNF)-1α, 1 HNF-1β, and 2 HNF-4α gene mutations.

Syndromic diabetes

There were 13 cases of syndromic diabetes; 69% (9 of 13) were classified as neonatal diabetes.

Incidence rates for non–type 1 diabetes and type 2 diabetes

No cases of type 2 diabetes and only one syndromic case were reported in the study period from the ROI; therefore, incidence data are given for U.K. alone. The U.K. population <17 years of age in mid-2004 was 12,440,700 (Office for National Statistics). The total number of confirmed cases of children with non–type 1 diabetes aged 0–16 years at diagnosis for the U.K. in 2004–2005 was 167 (excluding the 1 case from ROI), giving a national incidence of non–type 1 diabetes of $1.3 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$ (95% CI 1.2–1.6). For type 2 diabetes, the U.K. incidence was $0.53 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$ (0.41–0.68).

The incidence of type 2 diabetes was substantially higher in children from an ethnic minority background; $3.9 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$ (95% CI 2.1–6.7) and $1.25 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$ (0.6–2.4) for blacks and South Asians, respectively, compared with $0.35 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$ (0.2–0.5) for whites. (Incidence rates were calculated for cases reported in England only because mid-2004 estimates for ethnic groups were only available for that country.)

CONCLUSIONS — These data are the first to accurately quantify the U.K. incidence of type 2 diabetes in childhood. The only previously collected national data were prevalence data reported in 2004 (12). Given that the incidence data for our study are ~2.5 times higher than those of the prevalence data collected in 2003, this suggests that although ascertainment in the previous collection and our study may have been less than complete, we are witnessing an increase in childhood type 2 diabetic cases in this country. However, the overall incidence of type 2 diabetes in our survey ($0.53 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$) compared with the incidence of type 1 diabetes ($15–20 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$ in children <15 years) (26) indicates that type 2 diabetes is still relatively infrequent in our population. The incidence data for white children ($0.35 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$) are relatively similar to the only other available data from Europe (Austria; estimate of $0.25 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$). However, as in the U.S., some ethnic minorities are greatly overrepresented in our data (3). The incidence rates for South Asians and blacks are an alarming 3.5 and 11 times higher, respectively, than in whites. In some urban centers in the U.K., ethnic minorities make up 25–50% of the resident population, and there are indications that race does affect the prevalence of obesity (27), making specific health policies to address the etiology of type 2 diabetes in youth in these areas a matter of some urgency.

The lack of notified cases from the ROI at first glance might appear surprising. Although there are scant prevalence data for childhood obesity in the ROI, one recent report identified a prevalence of ~25% in a rural setting among primary school children (28), a value comparable to the U.K. Underreporting might be a factor causing this apparent anomaly, but, equally, the racial demographics of the ROI are different from the U.K., with only 1% of the population being of African or Asian extraction (29). Given ~900,000 individuals <17 years of age and a putative incidence similar to U.K. data for whites of $0.35 \cdot 100{,}000^{-1} \cdot \text{year}^{-1}$, the expected number would be slightly more than three new cases in the reporting period. This perhaps serves to exemplify the influence of racial heterogeneity on the national incidence of type 2 diabetes.

In terms of risk factors, the comparison between the U.K. and U.S. is surprisingly consistent. Overweight and obesity undoubtedly are major factors in type 2 diabetes etiology, and virtually all our cases were either obese or overweight, as previously described in the U.S. (30). Another major association in our type 2 diabetic cases was a family history of type 2 diabetes. The frequency of a history of type 2 diabetes in first- or second-degree relatives has ranged between 74 and 100% in the U.S. (3), and our findings (84%; 71% in first-degree relatives) mirror these findings. The mean age at presentation again reflects reports from the U.S. (30), with a peak around 13–14 years of age corresponding to late puberty in most adolescents and female subjects, on average, presenting ~1 year earlier than male subjects.

Acanthosis nigricans was identified in just over one-half of our type 2 diabetic cases, a lower value than that reported in the U.S. (31), where as many as 90% of individuals have this cutaneous manifestation of insulin resistance. The feature is said to be more common and more easily recognized in darker-skinned individuals, and this was certainly the case in our sample.

The U.K. is currently struggling to identify ways to reduce the year-by-year increase in obesity prevalence. Recent data from a number of sources indicate that these levels continue to increase in the U.K. (2). Strategies for the prevention and treatment of childhood obesity require urgent evaluation and should possibly, given limited health care resources, be more specifically focused on cities with large ethnic minority groups. A further effective strategy to prevent childhood-onset type 2 diabetes might be to target obesity-management programs toward obese children with a strong family history of the condition.

The limitations of our study largely stem from the framework within which the BPSU functions. Although response rates for this study were high at 94%, data collection relied on notification by pediatricians, some of whom may not have recognized the presence of type 2 diabetes in their patients. This may have led to an underestimation of the real incidence of type 2 diabetes. In an attempt to alert clinicians to the possibility of non–type 1 diabetes occurring in childhood, and especially to consider the possibility of type 2 diabetes, an information sheet was sent to all participating pediatricians at the start of the reporting period. The sheet detailed the clinical features suggestive of non–type 1 diabetes and alerted pediatricians to clinical presentations (e.g., antibody positivity) that, although traditionally typical of type 1 diabetes, may also occur in type 2 diabetes. To maximize case ascertainment, all clinicians reporting cases were sent a list of cases they had notified at the end of the reporting period and asked to check whether any eligible cases had been overlooked. Furthermore, the structure and ethical requirements of such epidemiological studies preclude directly requesting samples from all children for antibody or fasting insulin/C-peptide analysis; therefore, we had incomplete data on a number of children and were not able to accurately classify them. Moreover, our classification criteria might also have led to an underestimation of type 2 diabetes incidence due to our decision to exclude any cases presenting with ketosis at diagnosis if there was no direct evidence of hyperinsulinemia/absence of autoimmunity. It is now well documented that ketosis at diagnosis is a fairly common occurrence, especially in some racial groups, such as African Americans (32,33), and indeed 28% of our "definite cases" had evidence of ketosis at diagnosis. It is of course also possible that some of our unclassified cases (due to limited information provided) might have had type 2 diabetes. Despite these issues, we now have baseline data on which to construct a clearer image of the epidemiology of type 2 diabetes in childhood, with a repeat survey planned in 5 years. The incidence data are liable to be an underestimate of the true data, given the constraints and consequent limitations of our survey as documented above.

However, we present evidence that type 2 diabetes, although rare, is becoming increasingly prevalent in childhood in the U.K. Risk factors are similar to those in the U.S., with increasing adiposity, racial origin, and heredity all increasing risk. Children with type 2 diabetes tend to have other associated features, such as visceral obesity, dyslipidemia, and hypertension (i.e., the metabolic syndrome) (34). In all probability, this increases the risk of medium- to long-term complications compared with children developing type 1 diabetes.

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