The Incidence of Type 1 Diabetes in the Age Group 0–39 Years Has Not Increased in Antwerp (Belgium) Between 1989 and 2000

Evidence for earlier disease manifestation

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OBJECTIVE — A worldwide increase in the incidence of childhood type 1 diabetes has been observed. Because in various countries the majority of new type 1 diabetic patients are diagnosed in adulthood, we investigated whether the rising incidence of this disorder in children reflects a global increase in the incidence of diabetes or a shift toward earlier clinical presentation.

RESEARCH DESIGN AND METHODS — The incidence of type 1 diabetes presenting before age 40 years was prospectively measured in the Antwerp district over a 12-year period (1989–2000). The completeness of ascertainment was evaluated by the capture-recapture method. Trends in incidence during the study period were analyzed by Poisson regression.

RESULTS — The incidence of type 1 diabetes diagnosed before age 40 years remained constant over the 12-year period, averaging 9.9 cases per 100,000 individuals per year. The incidence was similar in both sexes under age 15 years, but a marked male excess was noted for adult-onset disease, in particular after age 20 years, resulting in a male-to-female ratio of 0.9 under age 15 years vs. 1.6 thereafter ($P = 0.001$). During the 12-year observation period, there was a significant tendency toward increasing incidence under age 15 years at the expense of a decreasing incidence between ages 15 and 40 years ($P = 0.025$). The annual increase in incidence averaged 1.8% under age 15 years and 5.0% under age 5 years ($P = 0.06$).

CONCLUSIONS — Our results indicate that in Belgium, the increasing incidence of childhood type 1 diabetes—especially for children under age 5 years—is not attributable to a global increase in disease incidence, but rather to earlier clinical manifestation. The results suggest that an environmental factor may preferentially accelerate the subclinical disease process in young diabetes-prone subjects.

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Abbreviations: BDR, Belgian Diabetes Registry; DIAMOND, DIAbetes MONDiale study; EURODIAB, EUROpe and DIABetes study; IAA, insulin autoantibody; IDA, Insulin-dependent Diabetes in young Adults study; GADA, glutamate decarboxylase antibody; RR, risk ratio.

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

Type 1 diabetes is believed to be caused by an immune-mediated destruction of pancreatic β-cells triggered by environmental factors in genetically susceptible individuals (1,2). Several reports have indicated a rapid increase in the incidence of childhood type 1 diabetes worldwide, especially in children under age 5 years (3–6). The most striking increase has been observed in Finland, which has the highest incidence of type 1 diabetes in the world (4,6). Apart from supporting the importance of environmental factors in the etiology of the disease (4,5), these observations also raise serious concerns about the possibility of an increasing burden of diabetes in the next decades. Indeed, patients diagnosed in early childhood are at high risk for developing chronic diabetes complications (7).

Most diabetes registries have studied disease incidence under age 15 years (4–6,8). In the rare instances when older age groups were studied in parallel, it was found that despite an incidence peak around puberty, the majority of new type 1 diabetic patients are diagnosed in adulthood, with a marked male preponderance (9–13). Thus, the question of whether the rising incidence of childhood type 1 diabetes is part of a global increase in incidence or the expression of a shift toward an earlier clinical presentation has remained unanswered. In the latter eventuality, it should be investigated whether such a shift affects both sexes equally. To address this question, we studied the prospective registration of incident cases of type 1 diabetes presenting before age 40 years in the Antwerp district (Belgium) during a 12-year observation period.

RESEARCH DESIGN AND METHODS

Subjects

The Antwerp district is a geographically defined region that is situated in the

northern part of Belgium with a total surface area of 1,000 km^2 and an average population density of 930 inhabitants per square kilometer (14). During the period 1989–2000, the population size of individuals ages 0–39 years averaged 488,457, based on annual civil registration numbers (14). Those numbers were also used to calculate the male-to-female ratio in the background population and as the denominator for the incidence rates.

During a 12-year study period (1 January 1989 to 31 December 2000), 571 type 1 diabetic patients residing in the Antwerp district and diagnosed before age 40 years were prospectively registered. Registration of newly diagnosed type 1 diabetic patients in the Belgian Diabetes Registry (BDR) is based on voluntary reporting by pediatricians and endocrinologists participating in the BDR, a national data and sample bank for recent-onset diabetic patients and their first-degree relatives under age 40 years. Diabetic patients were diagnosed as type 1 according to National Diabetes Data Group criteria (15). They resided in Antwerp for at least 6 months before clinical onset of diabetes (10). All patients were being treated with insulin; cases secondary to other conditions (e.g., cystic fibrosis, pregnancy, high-dosage steroid treatment) were excluded. Completeness of registration was assessed by the capture-recapture method, which assumes the availability of independent primary and (a combination of) secondary sources (16). By cross-classifying subjects according to their presence or absence in the primary and at least one of the secondary sources, the degree of completeness was estimated according to the method of Bishop et al. (17). Pediatricians and endocrinologists participating in the BDR constituted the primary source of ascertainment; the independent, secondary source of ascertainment was a combination of reporting by general practitioners and diabetes nurses; the Antwerp branch of the Flemish Diabetes Association; and self-reporting by patients (through voluntary participation in a nationwide family study on "Early Diagnosis and Prevention of Diabetes"). The ascertainment rates averaged 96% in the age group 0–14 years and 90% in the age group 15–39 years, and did not change significantly during the observation period.

The epidemiological survey in Antwerp was conducted within the framework of the EUROpe and DIABetes (EURODIAB) ACE and TIGER studies (ages 0–14 years; coordinators: A. Green, University of Aarhus, Denmark, and G. Soltész, University of Pècs, Hungary) and of the Insulin-dependent Diabetes in young Adults (IDA) study (ages 15–39 years; coordinator: K.O. Kyvik, University of Odense, Denmark). To adjust for differences in age and sex between populations and to ensure mutual comparability, directly standardized rates were calculated for the sexes separately and combined, as in the EURODIAB protocol. The common virtual standard population assumes equal numbers in each of the 5-year age categories for each sex.

We determined that 93% of patients diagnosed under age 15 years and 81% of patients diagnosed between ages 15 and 39 years tested positive for at least one type of diabetes-associated autoantibody (directed against islet cell cytoplasm, insulin, IA-2 protein, and/or glutamate decarboxylase) (18). The antibody assays repeatedly achieved 100% diagnostic sensitivity, specificity, and validity in the proficiency testing of the University of Florida (Gainesville, FL) and Louisiana State University (New Orleans, LA). In the combinatorial islet autoantibody workshop (19), assay sensitivity amounted to 73% for islet cell antibody, 36% for insulin autoantibody (IAA), and 85% for glutamate decarboxylase antibody (GADA); IA-2A antibody was not yet available in our laboratory at the time of the workshop (i.e., 1995).

The study was approved by the ethical committees of the universities participating in the scientific projects of the BDR, and informed consent was obtained from each subject and/or his/her parents in accordance with the Helsinki Declaration.

Statistical analysis

Differences between groups were assessed by Mann-Whitney *U* test for continuous variables and by χ^2 test with Yates'correction or Fisher's exact test, when appropriate, for discontinuous variables. Poisson regression models were used to investigate trends in incidence rate according to age group (0–4, 5–14, 0–14, and 15–39 years), sex, and calendar year and interactions among these variables. Two-tailed statistical tests were performed using SPSS for Windows 10.0 (SPSS, Chicago, IL) for personal computers or STATA for Poisson regression analysis (STATA, College Station, TX). Results were considered significant at $P < 0.05$.

RESULTS

Incidence rates according to age and sex

Between 1 January 1989 and 31 December 2000, 571 residents of the Antwerp district were reported to have developed type 1 diabetes before age 40 years. Figure 1 shows the mean incidence according to age at diagnosis for male and female patients diagnosed during the entire 12-year observation period. In childhood, the incidence was similar in boys and girls, with a peak value between ages 10 and 15 years; thereafter, the incidence tended to decrease more with age in women than in men, especially after age 20 years. To facilitate comparison of our results with other epidemiological studies, such as the EURODIAB (6), IDA (20) (both sponsored by European Union), and DIAbetes MONDiale (DIAMOND; sponsored by the World Health Organization) studies, patients were classified into two age categories for time of diagnosis: 0–14 and 15–39 years. In male subjects, the incidence of type 1 diabetes was similar in the two age groups and averaged 10.8/100,000 per year (Table 1). In the 0- to 14-year-old age group, the disease incidence in girls was slightly, though not significantly, higher than that in boys. In contrast, for diagnosis after age 15 years, the incidence was significantly lower in women than in men ($P < 0.001$) (Table 1). Between 1989 and 2000, the age- and sex-standardized incidence rate (95% CI) of the disease averaged 9.9/100,000 per year (CI 9.1–10.8) in the age category 0–39 years between 1989 and 2000. Overall, the disease incidence was similar in male and female subjects under age 40 years (Table 1). Regardless of sex, the incidence rate in the age group 0–14 years was slightly higher than in the older group ($P < 0.001$) (Table 1). The majority of the patients (342 of 571 or 60%) were diagnosed after age 15 years; in this adult-onset group, the male-to-female ratio (1.63) was strikingly increased ($P < 0.001$) compared to the male-to-female ratio in the background population (1.04) in the age group 15–39 years and to the value in patients diagnosed under age 15 years (0.92). Altogether, there was a slight male excess for diagnosis under age 40

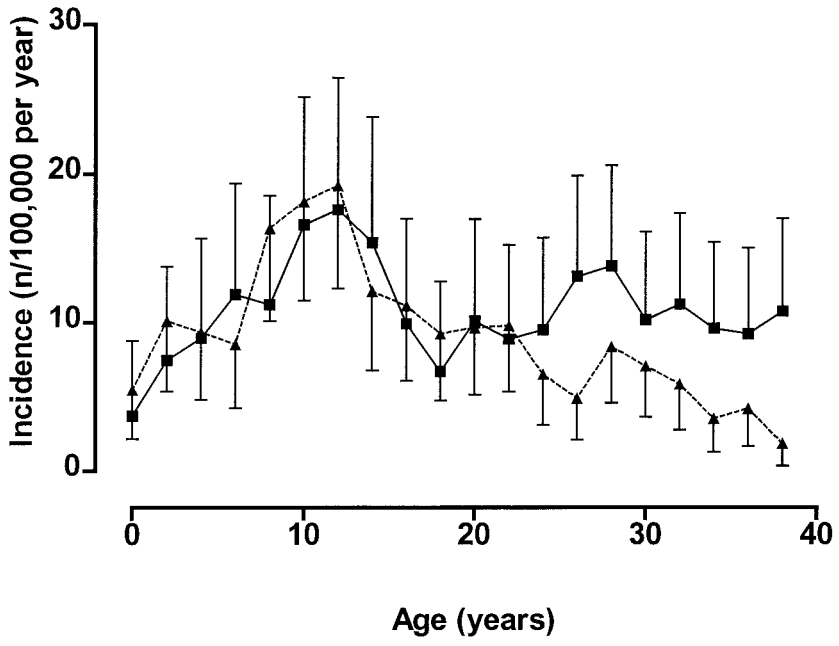

Figure 1—*Incidence of type 1 diabetes in the Antwerp district according to age at diagnosis (2-year age groups) and sex during a 12-year observation period (1989–2000). ▲, female patients; ■, male patients. Whiskers indicate lower or upper part of 95% CI.*

years (1.29; $P = 0.01$) (Table 1). The sex- and age-dependent differences in diabetes incidence could not be attributed to differences in completeness of case ascertainment according to sex or age (Table 1).

Secular trends in incidence according to age and sex

The overall incidence of type 1 diabetes under age 40 years did not increase according to calendar year in the period 1989–2000 (Fig. 2*A*). However, comparison of the incidence in the age groups 0–14 (Fig. 2*B*) and 15–39 years (Fig. 2*C*) showed an increasing trend in the younger age group, but a decreasing trend in the older. These trends could not be explained by temporal changes in ascertainment levels over the study period (Fig. 2).

To further analyze secular trends in incidence according to age and sex, we performed Poisson regression analysis. There was a significant age-by-sex-interaction ($P = 0.002$) confirming the male predominance in older age groups (10). There was also a significant trend ($P = 0.025$) in the incidence of type 1 diabetes in the age group 0–14 years compared with in the age group 15–39 years, showing an overall annual increase of 1.8% (CI −2.0 to 5.7) under age 15 years and an annual decrease of 3.8% (CI 0.7–6.7) above that age (Table 2). In children, the increase tended to be most pronounced under age 5 years, where it averaged 5% (CI −3.7 to 14.5, $P = 0.06$) (Table 2). Preliminary observations suggested that the differences in incidence rates in patients under and over age 15 were primarily attributable to males subjects. The estimated trend in male subjects ages 0–14 years (risk ratio [RR] 1.05, CI 0.99–1.10) was significantly different from subjects ages 15–39 years (RR 0.96, CI 0.92–1.00, $P = 0.013$), whereas this trend was not significant in female subjects (age 0–14 years: RR 0.99, CI 0.94–1.05; ages 15–39 years: RR 0.97, CI 0.92–1.02; $P = 0.46$). However, the trend did not differ significantly between male and female subjects under age 15 years.

CONCLUSIONS — Our epidemiological survey in the Antwerp district documented that the global incidence of type 1 diabetes arising before age 40 years has not increased over a 12-year period in that region (1989–2000). In line with international epidemiological studies, such as EURODIAB (6), DIAMOND (8), and IDA (20), we classified our patients according to diagnosis before or after age 15 years. Because the increase in incidence of childhood diabetes has been reported to be most pronounced in children under age 5 years, we also studied this age group. The incidence of childhood-onset diabetes in Antwerp is intermediate in Europe, being three times higher than in Macedonia but four times lower than in Finland (6,10). The Belgian incidence rate is similar to reported values for the Netherlands, Ger-

Table 1—*Incidence of type 1 diabetes, number of patients, and completeness of case ascertainment according to age at diagnosis and sex in the Antwerp district between 1 January 1989 and 31 December 2000*

	Age at diagnosis (years)		
Characteristics	0–14	15–39	0–39
Standardized incidence rate (per 100,000/year)			
Male	11.1 (9.1–13.3)	10.6 (9.2–12.2)	10.8 (9.6–12.0)
Female	12.5 (10.3–14.9)	7.0 (5.9–8.3)*	9.1 (8.0–10.3)
All	11.8 (10.3–13.4)	8.8 (7.9–9.8)†	9.9 (9.1–10.8)
Number of patients			
Male	110	212	322
Female	119	130	249
Male-to-female ratio	0.92	1.63‡§	1.29‖
% Ascertainment			
Male	96 (92–100)	92 (88–95)	94 (91–96)
Female	95 (91–99)	88 (82–93)	92 (89–96)
All	96 (93–98)	90 (86–93)	93 (91–95)

Data are *n* or *n* (95% CI). Ascertainment determined by capture-recapture method. *$P < 0.001$ vs. male sex (ages 15–39 years) and vs. female sex (ages 0–14 years); †$P = 0.001$ vs. age 0–14 years; ‡$P < 0.001$ vs. age 0–14 years; §$P < 0.001$ vs. ratio in age-matched background population (1.04 [180,684/174,442]); ‖$P = 0.010$ vs. ratio in age-matched background population (1.04 [271,449/261,413]).

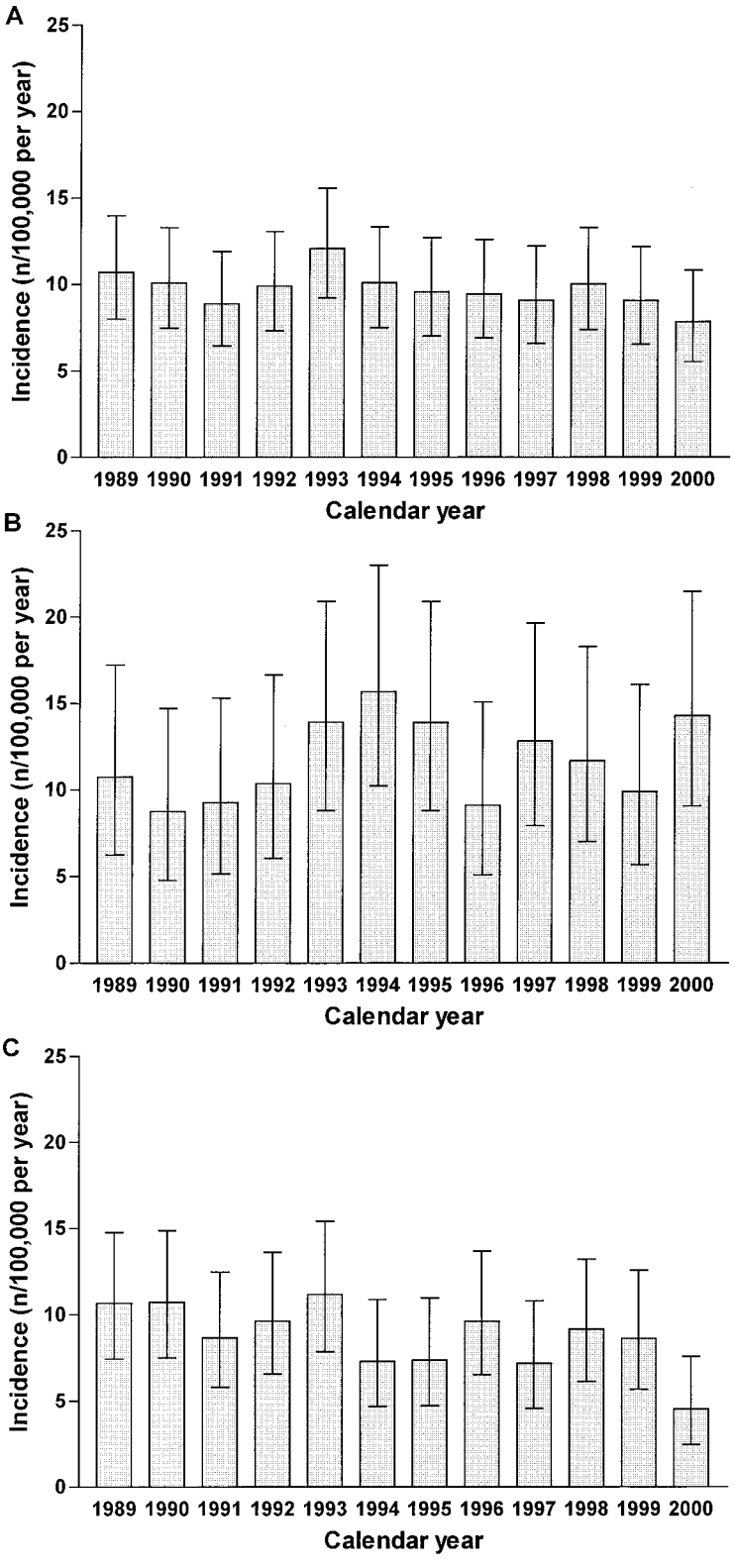

Figure 2—*Incidence of type 1 diabetes in the Antwerp district according to age group and calendar year (1989–2000) for ages 0–39 years* (A)*, 0–14 years* (B)*, and 15–39 years* (C)*. Whiskers indicate 95% CIs. Ascertainment rates amounted to 99% (CI 96–102) for 1989–1992, 99% (CI 97–101) for 1993–1996, and 87% (CI 79–94) for 1997–2000 in the age group 0–14 years, and to 90% (CI 85–95) for 1989–1992, 92% (CI 87–97) for 1993–1996, and 87% (CI 84–96) for 1997–2000 in the age group 15–39 years.*

many, and Luxembourg (6,10). In line with other observations in various countries throughout the world (3–6), we noted a tendency toward increasing incidence of childhood-onset type 1 diabetes, especially under age 5 years, during the 12-year observation period in Antwerp paralleled by a decreasing incidence of adult-onset disease. Although this trend is statistically significant, the overlapping CIs between the age groups considered indicated that the observed differences were borderline.

Although a secular trend toward increasing incidence of childhood type 1 diabetes has been reported throughout Europe in both boys and girls, differences according to age and sex were noted between countries (6). The shift toward earlier clinical manifestation of diabetes in the Antwerp district with near complete ascertainment was also confirmed in a larger representative group recruited nationwide during the same period (n = 2,831 of recent-onset Belgian type 1 diabetic patients) (10), but with incomplete case ascertainment (on average 50%) (Table 3) and tended to be restricted to male subjects in both Antwerp (see RESULTS) and nationwide (Table 3). The fraction of boys, but not of girls, diagnosed nationwide under age 15 years and in particular under age 5 years was significantly higher at the expense of the fraction of subjects diagnosed after age 15 years during the period 1995–2000 as compared to the period 1989–1994 ($P < 0.002$) (Table 3). There were no changes in age distribution of the background population during the same period, according to National Institute for Statistics data (14). Not surprisingly, there was a temporal trend toward an increasing male-to-female ratio in childhood-onset diabetes contrasting with a decreasing ratio in adult-onset disease (Table 3; $P = 0.024$). This is in line with results of an epidemiological study on childhood diabetes in Malta, reporting a selective decrease of age at diagnosis in boys (21).

The present study suggests that the increasing incidence of childhood diabetes may be due to an earlier clinical presentation rather than to a global rise in diabetes incidence in all age categories. It is conceivable that changes in early exposure to environmental factors may promote more rapid progression of the subclinical disease process to overt diabetes (22). This evolution is especially wor-

Table 2—*Summary of Poisson-regression analysis showing the incidence trend according to age at diagnosis during 1989-2000 in the Antwerp district*

Age group (years)	Risk ratio	χ^2	Degrees of freedom	*P*
0–14	1.02 (0.98–1.06)	5.04	1	0.025
15–39	0.96 (0.93–0.99)			
0–4	1.05 (0.96–1.15)	5.66	2	0.059
5–14	1.01 (0.97–1.05)			
15–39	0.96 (0.93–0.99)			

Data are *n* or *n* (95% CI).

rying because of the higher risk for devastating chronic complications in early-onset diabetes (7). A preliminary report from Sweden (23) also describes a decreasing incidence of diabetes diagnosed between age 15 and 35 years at the expense of an increase in incidence of childhood diabetes, suggesting that our observation is not restricted to Belgium but may have more general relevance. Furthermore, comparison of data from countries with diabetes registration up to at least age 29 years, has indicated that the fraction of adult-onset patients tends to be higher in countries with a low incidence of childhood-onset diabetes such as Romania as compared to high-incidence countries such as Sardinia or Sweden; it is conceivable that the observed large geographical differences in incidence of childhood-onset diabetes may at least in part be related to differences in age at diagnosis rather than to lifetime risk (9–13,16,20,23–25).

The present results also confirm a striking male-to-female excess in adult-onset diabetes, which contrasts with the strong female preponderance in other autoimmune diseases (26) and could relate to sex-specific differences in lifestyle, hormonal status, metabolic demands, or genetic susceptibility (8,10,11,24,25). Sex-dependent differences in incidence of type 1 diabetes have, so far, mostly been studied in patients diagnosed before age 15 years (8). In childhood diabetes, the male-to-female ratio has been reported to vary with the incidence level of the population under study. A slight excess of male patients was more often noted in high incidence countries whereas a slight female excess was observed in low incidence countries. In the present study, the male-to-female ratio approximated 0.9 for patients diagnosed under age 15 years, which agrees well with the observed range throughout Europe (0.7–1.3) (8) and the intermediate incidence rate of childhood diabetes in Belgium (6,10).

The tendency of disease incidence and male-to-female ratio to rise in parallel in young Belgian patients is also consistent with the positive correlation between male-to-female ratio and incidence levels in childhood diabetes noted throughout the world (8), and may suggest that a sex-related environmental factor is preferentially predisposing male subjects to rapid diabetes onset. Future research should confirm this observation in other populations and should try to identify this putative selective accelerator of subclinical diabetes in male subjects in the perspective of developing primary prevention (2). Because puberty and pregnancy are believed to precipitate clinical presentation of type 1 diabetes (22,27), an increased metabolic burden on β-cells could represent such an accelerator. Rapid growth rate, cold climate, acute infection, and psychological stress have all been suggested as risk factors for type 1 diabetes increasing the β-cell workload (28). Moreover, experimental studies have shown a rise in islet autoantigen expression in response to increased β-cell metabolism (29). In line with these findings, obesity has recently been proposed as a risk factor for childhood type 1 diabetes (30). The increasing prevalence of childhood obesity (31) and the reported association between (changes in) BMI and autoimmune markers in prediabetic children (32), in male first-degree relatives of diabetic patients (25), and in male middle-aged glucose-intolerant subjects from the general population (33) support the hypothesis that increased metabolic β-cell activity because of obesity and associated insulin resistance—especially in the case of android visceral obesity—constitutes an important effector of the shift toward earlier clinical presentation of not only type 2 but also of type 1 diabetes (34,35). In this respect, it is interesting to note that throughout Europe there is a large male-to-female excess in overweight individuals, with the highest prevalence being noted in Scandinavia and the U.K. (36). In contrast, a striking

Table 3—*Age distribution of male and female type 1 diabetic patients recruited by the Belgian Diabetes Registry and male-to-female ratio during two consecutive 6-year periods throughout Belgium*

	Male			Female			Male-to-female ratio		
Age at diagnosis (years)	1989-1994 (%)	1995-2000 (%)	*P*	1989-1994 (%)	1995-2000 (%)	*P*	1989-1994	1995-2000	*P*
n	673	970	—	489	699	—	—	—	—
0–4	6 (5)	10 (8)	0.004	9 (9)	10 (11)	0.839	0.89	1.44	0.095
5–14	29 (25)	32 (32)	0.234	38 (37)	39 (39)	0.661	1.05	1.12	0.664
15–39	65 (71)	58 (60)	0.005	53 (54)	51 (50)	0.546	1.69	1.58	0.544

Figures between brackets indicate the percentage observed in the Antwerp district where, in view of the low numbers, significance was not reached. Overall χ^2 test in male subjects, $P = 0.002$; overall χ^2 test in female subjects, $P = 0.800$; overall χ^2 test for male-to-female ratio, $P = 0.024$. Age distribution in background population for male and female subjects remained constant in both periods: ages 0–4 years, 11%; ages 5–14 years, 22%; ages 15–39 years, 67%. Completeness of registration compared to the Antwerp district with >90% ascertainment: 1989–1994, 36% for male patients vs. 31% for female patients; 1995–2000, 56% for male vs. 52% for female patients.

female-to-male excess exists in underweight subjects, with the highest frequencies of severely underweight women being noted in Luxembourg and Belgium (36).

In conclusion, this study showed that in Belgium, the increasing incidence of childhood type 1 diabetes, especially under age 5 years, is not attributable to a global increase in disease incidence, but rather to earlier clinical manifestation. The results suggest that an environmental factor may preferentially accelerate the subclinical disease process in diabetes-prone subjects. The possible implication of childhood obesity may create perspectives for prevention.

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References

1. Bingley PJ, Bonifacio E, Gale EAM: Can we predict IDDM? *Diabetes* 42:213–220, 1993
2. Slover RH, Eisenbarth GS: Prevention of type 1 diabetes and recurrent β-cell destruction of transplanted islets. *Endocr Rev* 18:241–258, 1997
3. Gardner SG, Bingley PJ, Sawtell PA, Weeks S, Gale EAM, the Bart's-Oxford Study Group: Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time trend analysis. *BMJ* 315:713–717, 1997
4. Onkamo P, Väänänen S, Karvonen M, Tuomilehto J: Worldwide increase in incidence of type 1 diabetes: the analysis of data on published incidence trends. *Diabetologia* 42:1395–403, 1999
5. Rewers M, LaPorte RE, Walczak M, Dmochowski K, Bogaczynska E: Apparent epidemic of insulin-dependent diabetes mellitus in midwestern Poland. *Diabetes* 36:106–113, 1987
6. EURODIAB ACE Study Group: Variation and trends in the incidence of childhood diabetes in Europe. *Lancet* 355:873–876, 2000
7. DeFronzo RA: Diabetic nephropathy: etiology and therapeutic considerations. *Diabetes Rev* 3:510–547, 1995
8. Karvonen M, Pitkäniemi M, Pitkäniemi J, Kohtamäki K, Tajima N, Tuomilehto J, for the World Health Organization DIAMOND Project Group: Sex difference in the incidence of insulin-dependent diabetes mellitus: an analysis of the recent epidemiological data. *Diabetes Metab Rev* 13: 275–291, 1997
9. Krolewski AS, Warram JH, Rand LI, Kahn CR: Epidemiologic approach to the etiology of type 1 diabetes mellitus and impaired glucose tolerance in adults. *N Engl J Med* 317:1390–1398, 1987
10. Vandewalle CL, Coeckelberghs MI, De Leeuw IH, Du Caju MV, Schuit FC, Pipeleers DG, Gorus FK, the Belgian Diabetes Registry: Epidemiology, clinical aspects, and biology of IDDM patients under age 40 years. *Diabetes Care* 20:1556–1561, 1997
11. Zimmet PZ: The pathogenesis and prevention of diabetes in adults. *Diabetes Care* 18:1050–1064, 1995
12. Mølbak AG, Christau B, Marner B, Borch-Johnsen K, Nerup J: Incidence of insulin-dependent diabetes mellitus in age groups over 30 years in Denmark. *Diabet Med* 11: 299–303, 1994
13. Bruno G, Merletti F, Vuolo A, Pisu E, Giorno M, Pagano G: Sex differences in incidence of IDDM in age-group 15–29 years: higher risk in males in province of Turin, Italy. *Diabetes Care* 16:133–136, 1993
14. Jaarlijkse Bevolkingsstatistieken (Annual Population Statistics): National Institute of Statistics, Brussels, Belgium, 1989–2000
15. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
16. LaPorte RE, Tajima N, Kerblom HK, Berlin N, Brosseau J, Christy M, Drash AL, Fishbein H, Green A, Hamman R, Harris M, King H, Larin Z, Neil A: Geographic differences in the risk of insulin-dependent diabetes mellitus: the importance of registries. *Diabetes Care* 8 (Suppl. 1):101–107, 1985
17. Bishop YMM, Fienberg SE, Holland PW: Estimating the size of a closed population. In *Discrete Multivariate Analysis: Theory and Practice*. Cambridge, MA, MIT Press, 1975, p. 231–233
18. Gorus FK, Goubert PG, Semakula C, Vandewalle CL, De Schepper J, Scheen A, Christie MR, Pipeleers DG, the Belgian Diabetes Registry: IA-2 autoantibodies complement GAD65-autoantibodies in new-onset IDDM patients and help predict impending diabetes in their siblings. *Diabetologia* 40:95–99, 1997

19. Verge CF, Stenger D, Bonifacio E, Colman P, Pilcher C, Bingley P, Eisenbarth GS, participating laboratories: Combined use of autoantibodies (IA2ab, GADab, IAA, ICA): combinatorial islet autoantibody workshop. *Diabetes* 47:1857–1866, 1998
20. Kyvik KO, Nyström L, Gorus F, Songini M, Barak L, Burton P, Castell C, Ionescu-Tirgoviste C, McKinney P, Ostrauskas R, Östman J: Incidence of type 1 diabetes in young adults across Europe: an EU funded multicentre study IDA. *Diabetologia* 44 (Suppl. 1):A75, 2001
21. Schranz AG: Trends in the incidence of childhood type 1 diabetes in Malta. *Diabetes Care* 21:194–195, 1998
22. Leslie RDG, Taylor R, Pozzilli P: The role of insulin resistance in the natural history of type 1 diabetes. *Diabet Med* 14:327–331, 1997
23. Pundziute-Lyckå A, Dahlquist G, Nyström L for the Swedish Childhood Diabetes Study and Diabetes Incidence Study in Sweden Group: The incidence of insulin-dependent diabetes has not increased in the 0–34 years group in Sweden 1983–1998. *Diabetologia* 44 (Suppl 1):A374, 2001
24. Cucca F, Goy JV, Kawaguchi Y, Esposito L, Merriman ME, Wilson AJ, Cordell HJ, Bain SC, Todd JA: A male-female bias in type 1 diabetes and linkage to chromosome Xp in MHC HLA-DR3-positive patients. *Nat Genet* 19:301–302, 1998
25. Weets I, Van der Auwera BJ, Schuit FC, Du Caju MVL, Decochez K, Coeckelberghs M, De Leeuw I, Keymeulen B, Mathieu C, Rottiers R, Dorchy H, Gorus FK, the Belgian Diabetes Registry: Male-to-female excess in diabetes diagnosed in early adulthood is not specific for the immune-mediated form nor is it HLA-DQ restricted: possible relation to increased body mass index. *Diabetologia* 44:40–47, 2001
26. Whitacre CC, Reingold SC, O'Looney PA, Task Force on Gender, Multiple Sclerosis and Autoimmunity: A gender gap in autoimmunity. *Science* 283:1277–1278, 1999
27. Buschard K, Buch I, Mølsted-Pedersen L, Hougaard P, Kühl C: Increased incidence of true type 1 diabetes acquired during pregnancy. *BMJ* 294:275–279, 1987
28. Dahlquist G: Hypothesis. Etiological aspects of insulin-dependent diabetes: an epidemiological perspective. *Autoimmunity* 15:61–65, 1993
29. Björk E, Kämpe O, Andersson A, Karlsson F: Expression of the 64kDa/glutamic acid decarboxylase rat islet cell autoantigen is influenced by the rate of insulin secretion. *Diabetologia* 35:490–3, 1992
30. Hyppönen E, Virtanen SM, Kenward MG, Knip M, Åkerblom HK, the Childhood Diabetes in Finland Study Group: obesity, increased linear growth, and risk of type 1 diabetes in children. *Diabetes Care* 23:1755–1760, 2000
31. Friedman JM: Obesity in the new millennium. *Nature* 404:632–634, 2000
32. Bruining GJ for the Netherlands Kolibrie Study Group on Childhood Diabetes: Association between infant growth before onset of juvenile type-1 diabetes and autoantibodies to IA-2. *Lancet* 356:655–656, 2000
33. Rolandsson O, Hägg E, Hampe C, Sullivan EP, Nilsson M, Jansson G, Hallmans G, Lernmark Å: Glutamate decarboxylase (GAD65) and tyrosine phosphatase-like protein (IA-2) autoantibodies index in a regional population is related to glucose intolerance and body mass index. *Diabetologia* 42:555–559, 1999
34. Wilkin TJ: The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. *Diabetologia* 44:914–922, 2001
35. Gorus FK, Weets I, Pipeleers DG: Increased metabolic burden on the beta cells and acceleration of diabetes onset. *Diabetologia* 45:288–289, 2002
36. Eurostat: Key data on Health. Health in the EU under the microscope. [article online] Eurostat News Release no. 103, 8 September 2000. Available from http://europa.eu.int/comm/eurostat.html