ORIGINAL ARTICLE

β-cell autoantibodies in children with type 2 diabetes mellitus: subgroup or misclassification?

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Arch Dis Child 2006;**91**:473–477. doi: 10.1136/adc.2005.088229

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Accepted 6 January 2006
Published Online First 31 January 2006

Background: In adults, a fraction of diabetic individuals with β-cell autoantibodies has initially non-insulin requiring diabetes clinically appearing as type 2 diabetes mellitus (T2DM), named latent autoimmune diabetes in adulthood (LADA). The occurrence of β-cell autoantibodies in European children and adolescents with T2DM has not been reported so far.
Methods: The frequency of β-cell autoantibodies (anti-GAD, anti-IA-2, and anti-ICA) was determined in 7050 diabetic children and adolescents. The type of diabetes was classified by paediatric diabetic specialists based on the clinical presentation. Children with non-insulin dependent T2DM over a one year period were studied separately.
Results: A total of 6922 children were clinically classified as having type 1 diabetes (T1DM) and 128 children as having T2DM. Thirty six per cent of the children with T2DM had at least one detectable β-cell autoantibody. These children did not differ significantly from the children with T2DM and without autoantibodies in respect of age, gender, weight status, lipids, blood pressure, C-peptide, glucose, and HbA1c at manifestation, as well as frequency of anti-thyroidal antibodies and insulin treatment during follow up. In the subgroup of the 38 children with T2DM without insulin requirement over a one year period, autoantibodies occurred in 32%. These 12 children were predominantly obese (67%), female (67%), and in the pubertal age range.
Conclusion: β-cell autoantibodies were detectable in a subgroup of initially non-insulin dependent diabetic children and adolescents with the clinical appearance of T2DM. Following the terminology ''latent autoimmune diabetes in adulthood (LADA)'', this subgroup might be classified as ''LADY'' (latent autoimmune diabetes in youth).

Recent reports indicate an increasing incidence of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) in children and adolescents.[1 2] T1DM is characterised by insulin dependency, in contrast to T2DM, in which there is a relative insulin deficiency with a variable degree of insulin resistance.[1] Typically, children with T1DM are not overweight and have a short duration of symptoms. In contrast, individuals with T2DM seldom manifest with ketosis, have few symptoms, are usually obese, and have the clinical features of insulin resistance.[1 3]

In some patients, a clinical differentiation between T1DM and T2DM is not possible at manifestation and autoantibodies are used to define the type of diabetes.[1 3] The American Diabetes Association recommends declaring children with diabetes and autoantibodies as T1DM regardless of their insulin dependency.[1] Three small studies in the USA based on <50 children reported β-cell autoantibodies in 10–74% of children with T2DM, depending on ethnic background.[4–6] Data concerning the frequency of autoantibodies in European children and adolescents with T2DM have not been reported so far. Therefore, the aim of this study was to analyse a large cohort of European children clinically classified as T2DM for the occurrence of β-cell autoantibodies and to describe the clinical presentation of children with T2DM who are positive for β-cell antibodies.

METHODS

A computer program based on the foxpro 7.0 compiler was developed for standardised prospective documentation of children and adolescents with diabetes mellitus.[7] Besides anthropometric parameters, metabolic control and treatment modalities are documented longitudinally by the software. The software allows standardised patient reports as well as local aggregation of data and patient selection according to multiple criteria. Anonymised data are transmitted for central analysis. Each participating centre complies with local ethical and data management guidelines. Inconsistent data are reported back to the centres twice a year for correction.

Ninety five treatment centres for diabetic children and adolescents in Germany participated in this study. This report takes into account data from 7050 children and adolescents aged 1–19 years accumulated between 1995 and 2004 in which the measurement of at least one β-cell autoantibody and the antidiabetic regime was documented.

The weight status was recorded as body mass index (BMI) and the BMI standard deviation score (SDS-BMI) using the LMS method:[8] The M and S values correspond to the median and coefficient of variation of BMI for German children of each age and gender, whereas the L value allows for the substantial age dependent skewness in the distribution of BMI.[8 9] The assumption underlying the LMS method is that after Box–Cox power transformation the data are normally

Abbreviations: anti-IAA, autoantibodies to insulin; anti-GAD, autoantibodies to glutamic acid decarboxylase; anti-ICA, autoantibodies to islet cells; anti-IA-2, autoantibodies to protein tyrosine phosphatase IA-2; anti-TPO, autoantibodies to thyroid peroxidase; anti-TAK, autoantibodies to thyreoglobulin; BMI, body mass index; HbA1c, glycosylated haemoglobin; IQR, interquartile range; LADA, latent autoimmune diabetes in adulthood; LADY, latent autoimmune diabetes in youth; SDS, standard deviation score; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Table 1 Clinical characteristics of children classified as T1DM or T2DM at diagnosis

	T1DM	T2DM	p value
Number	6922	128	
Age	9.3 (5.7 to 12.3)	13.7 (11.9 to 15.3)	<0.001
Gender	47% girls	63% girls	<0.001
Non-German origin	8%	13%	0.028
BMI	19.8 (17.4 to 22.8)	30.4 (26.1 to 34.9)	<0.001
SDS BMI	0.64 (0.06 to 1.26)	2.30 (1.72 to 2.93)	<0.001
SDS weight	0.54 (−0.07 to 1.17)	2.12 (1.25 to 3.05)	<0.001
HbA1c (%)	9.0 (7.6 to 11.1)	7.8 (6.3 to 10.4)	<0.001
Glucose (mg/dl)	375 (246 to 516)	239 (129 to 324)	<0.001
pH ⩽7.3	6%	1%	0.044
C-peptide >1.5 ng/ml*	4%	31%	<0.001
Cholesterol (mg/dl)	170 (150 to 193)	183 (153 to 206)	0.038
HDL cholesterol (mg/dl)	60 (50 to 71)	41 (34 to 50)	<0.001
Triglycerides (mg/dl)	62 (91 to 135)	144 (66 to 220)	<0.001

Data presented as median (IQR) or percentages.
*Determined in the non-ketotic state.

distributed. Obesity was defined by a BMI >97th centile using population specific reference data.[9]

The local paediatric diabetic specialists defined the type of diabetes based on clinical presentation and family history. The diagnosis was confirmed by two independent experienced paediatric diabetologists according to the following criteria: manifestation with ketoacidosis (pH ⩽7.3), abruptness of onset of hyperglycaemic symptoms and weight loss, insulin deficiency (C-peptide values ⩽1.5 ng/ml[6]), and the perceived need for insulin replacement are compatible with T1DM. Besides obesity, clinical (acanthosis nigricans and hypertension) and laboratory signs of insulin resistance (hypertriglyceridaemia and low HDL cholesterol) point to T2DM. Children with monogenetic forms of diabetes, genetic syndromes, or secondary diabetes were excluded from the analysis. German origin was defined by both parents being born in Germany.

The following β-cell autoantibodies were determined by the respective referral labs and positively evaluated according to in-house reference cut-offs: autoantibodies to insulin (anti-IAA), glutamic acid decarboxylase (anti-GAD), islet cells (anti-ICA), protein tyrosine phosphatase IA-2 (anti-IA-2). Furthermore, antibodies against the thyroid peroxidase (anti-TPO) and thyreoglobulin (anti-TAK) were analysed. All laboratories participated in the Diabetes Antibody Standardisation Programmes and in workshops using sample exchange and cross-validation.[10] To identify outliers in the sensitivity of β-cell antibodies in the different labs, the frequency of autoantibodies in T1DM children in the different institutions were tested on normal distribution by the Kolmogorov–Smirnow test. Due to the possible induction of insulin antibodies by external insulin therapy, measurements of anti-IAA were only included before insulin therapy was initiated.

C-peptide, total cholesterol, HDL cholesterol, and triglycerides were analysed by commercially available kits at the participating centres. C-peptide levels were determined in the non-ketotic state. Cut-off points of 5.6 mmol/l (220 mg/dl) for total cholesterol, 0.9 mmol/l (35 mg/dl) for HDL cholesterol, and 1.7 mmol/l (150 mg/dl) for triglycerides were used to define dyslipidaemia according to international recommendations.[11] Hypertension was defined as blood pressure above the 95th centile in multiple measurements in accordance with the second task force report.[12] HbA1c values from different labs were mathematically standardised to the DCCT normal range (4.05–6.05%).

The children clinically classified as T2DM were divided into two groups according to presence or absence of autoantibodies. Age, gender, weight status, lipids, blood pressure, metabolic situation at manifestation, and frequency of insulin treatment during follow up were compared in these two groups. Furthermore, the children with T2DM treated without insulin over a period more than one year were analysed separately.

The SAS 9.1 statistical software package was used for descriptive data evaluation. Non-parametric statistical tests (Mann-Whitney U test/Wilcoxon test) were used. A p value <0.05 was considered as significant. Data are presented as median and interquartile range (IQR).

RESULTS

The clinical characteristics of children with T1DM and T2DM are shown in table 1. At manifestation, children with T2DM were significantly older, more obese, and predominantly female. Glucose and HbA1c were significantly lower in these children compared to children with T1DM, while ketoacidosis predominantly occurred in T1DM. The vast majority of children with T1DM were treated with insulin (T1DM 99% versus T2DM 37%, $p < 0.001$) and with higher doses of insulin (T1DM: median 0.87 (IQR 0.67–1.09) IE/kg body weight; T2DM: median 0.50 (IQR 0.37–0.74) IE/kg body weight; $p < 0.001$).

At least one positive β-cell autoantibody was detected in 36% of the children classified as T2DM, while 80% of the children with T1DM showed at least one β-cell autoantibody ($p < 0.001$). Anti-GAD was determined in 5059 children with T1DM and in 102 children with T2DM. Anti-IA-2 was measured in 3134 children with T1DM and in 66 children with T2DM. Measurements of anti-ICA were performed in 4894 children with T1DM and in 82 children with T2DM. Anti-GAD (T1DM 66% versus T2DM 16%, $p < 0.001$), anti-IA-2 (T1DM 66% versus T2DM 14%, $p < 0.001$), and anti-ICA (T1DM 52% versus T2DM: 6%, $p < 0.001$) autoantibodies occurred significantly more often in children with T1DM compared to children with T2DM. Anti-IAA, which was measured in 2847 children with T1DM and in 67 children with T2DM, were detectable in 53% of the children with T1DM and in 40% of the children with T2DM ($p = 0.037$). The frequency of autoantibodies in children with T1DM in the different institutions was normally distributed ($p = 0.785$).

Table 2 displays the clinical characteristics of children with T2DM divided by the presence or absence of β-cell autoantibodies. Children with β-cell autoantibodies did not differ significantly from children without β-cell autoantibodies in respect of age, gender, weight status, lipids, blood pressure, C-peptide, glucose, and HbA1c at manifestation. Furthermore, there was no significant difference between these two groups concerning the frequencies of hypertension (47% versus 32%, $p = 0.010$), dyslipidaemia (72% versus 65%,

Table 2 Clinical and laboratory characteristics at manifestation of children classified as T2DM separated accordingly to the presence of β-cell autoantibodies

	No β-cell autoantibodies	β-cell autoantibodies	p value
Number	82	46	
Age	13.9 (12.0 to 15.4)	13.0 (10.9 to 15.4)	0.365
Gender	66% girls	57% girls	0.237
Non-German origin	15%	11%	0.520
BMI	30.5 (25.6 to 35.3)	30.0 (26.1 to 34.9)	0.861
SDS BMI	2.28 (1.68 to 2.91)	2.39 (1.79 to 2.95)	0.635
SDS weight	2.10 (1.18 to 2.94)	2.15 (1.70 to 3.14)	0.428
HbA1c (%)	8.0 (6.3 to 10.7)	7.5 (6.3 to 10.4)	0.575
Glucose (mg/dl)	238 (149 to 314)	251 (121 to 330)	0.943
pH $\leqslant$7.3	2%	0%	0.287
C-peptide >1.5 ng/ml*	33%	28%	0.586
Cholesterol (mg/dl)	183 (155 to 211)	173 (146 to 198)	0.180
HDL cholesterol (mg/dl)	42 (34 to 52)	41 (36 to 49)	0.973
Triglycerides (mg/dl)	157 (96 to 248)	128 (95 to 186)	0.295
Systolic blood pressure (mm Hg)	135 (121 to 145)	131 (120 to 140)	0.570
Diastolic blood pressure (mm Hg)	80 (72 to 89)	78 (70 to 89)	0.334

Data presented as median (IQR) or percentages.
*Determined in the non-ketotic state.

p = 0.444), and anti-thyroidal antibodies (anti-TPO: 10% versus 8%, p = 0.762; anti-TAK: 9% versus 9%, p = 0.999).

In children with T2DM, the follow up period after manifestation of diabetes was 16 (IQR 3–35) months in those without β-cell autoantibodies and 15 (IQR 2–36) months in those with β-cell autoantibodies. Thirty seven per cent of these children without β-cell autoantibodies and 38% of these children with β-cell autoantibodies were treated with insulin during follow up. There were no differences between these two groups regarding the interval between the diagnosis of diabetes, the initiation of insulin treatment (p = 0.541), and the required insulin doses (insulin dose (IE)/body weight (kg): 0.50 (IQR 0.36–0.74) versus 0.52 (IQR 0.38–0.80); p = 0.551).

The observation period was more than one year in 65 patients classified as T2DM. Seventeen of the 43 (40%) children without β-cell autoantibodies and 10 of the 22 (45%) children with β-cell autoantibodies were treated with insulin (p = 0.649). In the subgroup of >1 year non-insulin dependent T2DM children (n = 38), β-cell autoantibodies were detectable in 12 (32%) children. Patients with β-cell autoantibodies did not differ from children without β-cell autoantibodies in respect of age, gender, lipids, blood pressure, C-peptide, glucose, and HbA1c at manifestation (table 3). Children with β-cell autoantibodies showed a tendency—but without significance—of higher weight (SDS weight, SDS BMI) compared to children without β-cell antibodies. The children with and without β-cell antibodies did not differ in their frequency of hypertension (25% versus 29%, p = 0.795) or dyslipidaemia (56% versus 65%, p = 0.617).

DISCUSSION

This is the first study reporting β-cell autoantibodies in European children and adolescents clinically appearing as T2DM. In our study of predominantly Caucasians, the children and adolescents with T2DM were older, more overweight, and predominantly female compared to the patients with T1DM in accordance with many studies in other ethnic groups.[1–3] Surprisingly, 36% of the children classified as T2DM had at least one positive β-cell autoantibody. This frequency was much higher than in a sample of healthy German schoolchildren, in which approximately 1% were positive for β-cell autoantibodies.[13] However, this frequency was in the range of 10–74% reported by the small studies in children and adolescents from the USA.[4–6] In addition to the small sample sizes, this large range can be probably be explained by the different ethnic backgrounds.[5]

It could be assumed that the children with autoantibodies were misclassified as T2DM since the presence of β-cell autoantibodies defines T1DM.[1] Most recently however, concerns have been raised that some of the children diagnosed with T2DM may have actually been misdiagnosed based on clinical features and actually represent obese children with autoimmune diabetes.[5 14 15] In accordance with this argument, the reported increase in clinically diagnosed T2DM might at least in part represent an increase of obese children with T1DM.[4]

Conversely, the absence of diabetes autoimmune markers may not be a prerequisite for the diagnosis of T2DM.[5 6] In the non-insulin dependent children over a period of more than one year, β-cell autoantibodies were as frequent (32%) as in the whole group of patients with T2DM. Non-insulin dependency over more than one year excludes absolute insulin deficiency in this time period as typically suspected in childhood T1DM. The possibility that positive β-cell antibodies in these non insulin-requiring diabetic children and adolescents represent a form of early-onset latent autoimmune diabetes similar to that described in adults (LADA)[16] needs to be considered.

Worldwide studies have identified 10–20% of diabetic patients with β-cell autoantibodies in non-insulin requiring adult diabetics.[17–19] Patients with LADA share insulin resistance with T2DM patients but display a more severe defect in β-cell capacity.[20] Following the terminology ''latent autoimmune diabetes in adulthood'', the non-insulin dependent diabetic children and adolescents with β-cell autoantibodies could be classified as ''latent autoimmune diabetes in youth'' (LADY).

The accelerator hypothesis postulates a shared basis for both T1DM and T2DM: besides individual predisposition and autoimmunity, insulin resistance is suggested to lead to β-cell insufficiency.[21 22] In the prediabetic period of an immune mediated destruction of β-cells, increasing insulin resistance can result in clinical diabetes.[16] Obesity and puberty are important factors for developing insulin resistance in childhood and adolescence.[23] In accordance with this, the children with LADY were predominantly pubertal and obese. Additionally, clinical features of insulin resistance such as dyslipidaemia and hypertension frequently appeared in these children.

In patients with LADA, autoimmune thyroiditis is often reported.[24 25] In our patients with LADY, there was only a low

Table 3 Clinical and laboratory characteristics at manifestation of non-insulin dependent children with duration of T2DM >1 year separated accordingly to the presence of β-cell autoantibodies

	No β-cell autoantibodies	β-cell autoantibodies	p value
Number	26	12	
Age	13.9 (11.7 to 15.0)	12.9 (12.1 to 13.8)	0.258
Gender	50% girls	67% girls	0.343
Non-German origin	8%	17%	0.408
BMI	29.0 (21.0 to 35.4)	29.5 (25.9 to 38.4)	0.198
SDS BMI	1.93 (0.59 to 2.73)	2.30 (1.64 to 3.10)	0.077
SDS weight	1.53 (0.34 to 2.56)	2.49 (1.56 to 3.39)	0.061
HbA1c (%)	6.4 (5.6 to 7.4)	6.2 (5.7 to 7.5)	0.877
Glucose (mg/dl)	212 (149 to 284)	232 (154 to 308)	0.987
C-peptide >1.5 ng/ml*	27%	25%	0.901
Cholesterol (mg/dl)	182 (155 to 206)	186 (166 to 193)	0.801
HDL cholesterol (mg/dl)	43 (33 to 51)	41 (36 to 53)	0.977
Triglycerides (mg/dl)	173 (76 to 248)	150 (124 to 220)	0.571
Systolic blood pressure (mm Hg)	122 (109 to 132)	127 (114 to 139)	0.298
Diastolic blood pressure (mm Hg)	68 (60 to 84)	72 (67 to 80)	0.687

*Determined in the non-ketotic state.

percentage of positive anti-thyroid antibodies. In adults, the types of β-cell autoantibodies can distinguish between acute onset T1DM and LADA because GAD antibodies and ICA antibodies indicate slow disease progression, whereas the presence of IA-2 antibodies is associated with an acute onset clinical phenotype.[25] Since all types of antibodies were detectable in both T1DM and LADY, the type of antibody does not seem to distinguish these two entities in children and adolescents.

Children with LADY did not differ from children with T2DM without β-cell autoantibodies in respect of age, gender, anthropometrical data, clinical features of insulin resistance, and glucose metabolism at manifestation. In conclusion, these two groups of patients can only be distinguished by measurement of β-cell antibodies.

Apart from β-cell autoantibodies in children clinically classified as T2DM, negative autoantibodies in children with T1DM with acute onset of diabetes, severe metabolic impairment, and insulin requirement only in the early stage of disease are reported.[1] T1DM and T2DM do not seem to be completely distinctive and can overlap considerably. Therefore, serology cannot completely distinguish these two types of diabetes.

Our study has some potential limitations. Since β-cell autoantibodies were determined in different laboratories, autoantibody titres are not comparable and cannot be correlated with clinical presentation. Furthermore, laboratories might differ in the sensitivity of their antibody detection. However, paediatric diabetologists in general practice resort to their local associated laboratories during routine care. The frequency of autoantibodies in T1DM children in the different laboratories showed a normal distribution excluding relevant outliers. Additionally, since not all β-cell antibodies were measured in all patients, we have to interpret the frequencies of β-cell antibodies cautiously. We can only conclude that the frequency of β-cell autoimmunity was at least 32% in children classified as T2DM. Finally, since obesity was partially used for the clinical definition of diabetes type, this could explain the high frequency of overweight in the patients classified as LADY in contrast to adult patients with LADA, which are usually not overweight.[16] Finally, data regarding insulin treatment in children and adolescents should be interpreted with caution. Patients could be misdiagnosed as having T1DM based on either age or diabetic ketosis at presentation. Moreover, social and cultural factors interfering with compliance with non-insulin regimens may lead to use of insulin in non insulin-requiring patients.

In summary, β-cell autoantibodies were present in a subgroup of initially non-insulin dependent diabetic children clinically appearing as T2DM. We propose that the presence of autoantibodies should not be used to exclude the diagnosis of T2DM in children and adolescents. Alternatively, a separate category in addition to T1DM and T2DM for patients sharing features of both T1DM and T2DM should be considered.[26] Large prospective paediatric diabetes studies with a longer follow up are needed to confirm the subgroup of T2DM children with autoimmune markers. Acceptance of this concept could open the door to trials with a broader range of therapeutic modalities for a group of children and adolescents who were previously labelled insulin dependent for life.

ACKNOWLEDGEMENTS

We thank the following centres for participating in this study: Aachen–Kinderklinik RWTH, Ahlen St Franziskus Kinderklinik, Aue Helios Kinderklinik, Augsburg Kinderklinik Zentralklinikum, Aurich Kinderklinik, Bad Hersfeld Kinderklinik, Bad Oeynhausen, Diabetesfachklinik, Berlin Kinderklinik Lindenhof, Berlin Klinik St Hedwig Innere, Berlin Virchow-Kinderklinik, Berlin-Hellersdorf–Innere, Bielefeld Kinderklinik Gilead, Bonn Uni-Kinderklinik, Bottrop Kinderklinik, Bottrop Knappschaftskrankenhaus–Innere, Bremen–Kinderklinik Nord, Bremen Kinderklinik St Jürgenstrasse, Bremen–Epidemiologieprojekt, Bremerhaven Kinderklinik, Bruckmühl Internist, Praxis, Celle Kinderklinik, Chemnitz Kinderklinik, Coesfeld Kinderklinik, Darmstadt Kinderklinik Prinz. Margareth, Datteln Kinderklinik, Deggendorf Kinderarztpraxis, Deggendorf Kinderklinik, Delmenhorst Kinderklinik, Detmold, Kinderklinik, Dortmund Kinderklinik, Dortmund-St Josefshospital Innere, Dresden Uni-Kinderklinik, Düren-Birkesdorf Kinderklinik, Düsseldorf Uni-Kinderklinik, Erfurt Kinderklinik, Erlangen, Uni-Kinderklinik, Essen Uni-Kinderklinik, Esslingen Städtische Kinderklinik, Eutin Kinderklinik, Eutin St-Elisabeth Innere, Freiburg Uni-Kinderklinik, Friedrichshafen Kinderklinik, Fulda Kinderklinik, Fürth Kinderklinik, Gaissach Kinder-Fachklinik, Garmisch-Partenkirchen Kinderklinik, Gelsenkirchen Kinderklinik Marienhospital, Gemeinschaftspraxis Rastatt, Gießen Uni-Kinderklinik, Göppingen Kinderklinik am Eichert, Görlitz Städtische Kinderklinik, Göttingen Uni-Kinderklinik, Hachenburg Kinderpraxis, Hagen Kinderklinik, Halle Uni-Kinderklinik, Halle-Dölau Städtisches Krankenhaus, Hamburg Altonaer Kinderklinik, Hamburg Kinderklinik Wilhelmstift, Hamburg-Nord Kinderklinik Heidberg, Hamm Kinderklinik, Hanau Kinderklinik, Hannover Henriettenstift–Innere, Hannover Universitätskinderklinik MHH, Hannover Kinderklinik auf der Bult, Heidelberg Uni-Kinderklinik, Heidenheim Kinderklinik, Heilbronn Innere Klinik, Herford Kinderklinik, Hermeskeis Kinderpraxis, Herzberg Kreiskrankenhaus Innere, Hildesheim Kinderarztpraxis, Hildesheim Kinderklinik, Hinrichsegen-Bruckmühl Diabetikerjugendhaus, Homburg Uni-Kinderklinik Saarland, Itzehoe Kinderklinik, Jena Uni-Kinderklinik,

What is already known on this topic

- A proportion of adult diabetic patients with β-cell autoantibodies are not initially insulin requiring and can mimic manifestation of type 2 diabetes

What this study adds

- At least 32% of the diabetic children and adolescents clinically presenting as type 2 diabetes, had at least one positive β-cell antibody titre

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Funding: this study received financial support by the German Ministry of Health, German Diabetes Association, German Research foundation (DFG), National Action For Diabetes Mellitus (NAFDM), German Diabetes Foundation, Dr-Bürger-Büsing-Foundation, and Novo Nordisk Germany

Competing interests: none declared

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