Epidemiological perspectives on type 1 diabetes in childhood and adolescence in Germany: 20 years of the DIARY registry

Stefan Ehahlt, MD¹, Klaus Dietz, PhD², Andre M. Willasch, MD³, Andreas Neu, MD¹ for the DIARY-Group* Baden-Wuerttemberg

*A complete list of DIARY-Group members can be found in the acknowledgements.

¹University Children’s Hospital, Tuebingen, Germany, ²Department of Medical Biometry, Eberhard-Karls-University, Tuebingen ³University Children’s Hospital, Frankfurt, Germany

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Corresponding author:
Dr Andreas Neu
E-mail: andreas.neu@med.uni-tuebingen.de

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Objective: To predict the frequency of type 1 diabetes in childhood and adolescence (<15 years of age) in Germany for the next 20 years.

Research Design and Methods: Data on diabetes onset has been collected by means of a registry in the Federal German state of Baden-Wuerttemberg (documentation period, 1987-2006; n=5,108; completeness of data 98.1%).

Results: The current incidence rate (2000-2006) is 19.4/100,000/year (95% CI 18.6-20.2). The annual incidence rate can be expressed as a square of a linear function of the calendar year x (y = (3.05+0.0778*(x-1986))^2, r^2 = 0.90). The highest increase per year was observed in the age groups comprising 2- and 3-year-olds (12% and 13% per year, respectively). The incidence rate for the year 2026 is estimated to be 37.9/100,000/year (95% CI 33.3-42.9).

Conclusions: The increase that we found in younger children is characteristic of a left shift towards an earlier age.
We present the statistics over 20 years pertaining to the frequency of type 1 diabetes among children and adolescents in the third largest state of Germany, which we derived from the Baden-Wuerttemberg incidence register. We developed a prediction model in order to predict the frequency of diabetes for the total group (0 to 14 years of age) for the next 20 years. These data are essential for health care planning. Additionally, they provide further insight into the epidemiology of the disease in our country over a forty-year period.

METHODS
Diabetes onset in children and adolescents below 15 years of age was documented according to the EURODIAB criteria (1). Data deriving from surveys done during meetings of independent patient groups were used as a secondary data source. The completeness of data at source was 98.1% (Capture-mark-recapture method) (2, 3).
In order to predict the total number of cases of diabetes onset in Baden-Wuerttemberg up to the year 2026, we developed a model as described below: The incidence rates followed a Poisson distribution. Thus, a square root transformation of the data from the total period of observation was done. This square root-converted incidence rate for each age was described as a linear function of the calendar year. The estimated values of the slopes and the intercepts were described by means of a polynomial with three parameters. We applied a cubic function for the slopes, and a 4th degree polynomial for the intercepts.

RESULTS
The current incidence rate (2000-2006) is 19.4/100,000/year (95% CI 18.6-20.2). The annual incidence rate can be expressed as the square of a linear function of the calendar year x (y = (3.05 + 0.0778*(x-1986))^2, r^2 = 0.90). Thus the incidence rate for the year 2026 is estimated to be 37.9/100,000/year (95% CI 33.3-42.9). Between 1987 and 2006 there were 5,108 children and adolescents who developed type 1 diabetes. In the following 20 years this figure is expected to rise to 7,600.
The prediction model based on the BW incidence register is as follows: (b0 + b1 * age + b3 * (age - 8) ^ 4 + (m0 + m1 * age + m3 * (age - 8) ^ 3) * year)^2; b0 = 2.11, b1 = 0.152, b3 = -0.00062, m0 = 0.132, m1 = -0.0069, m3 = 0.000124; age: 1 to 15, year: 1 to 20 (year 1 = 1987, year 20 = 2006).
The highest incidence rate was found among 10- to 14-year-olds (18.7/100,000/year, 95% CI 17.9-19.5), followed by ages 5 to 9 (16.5/100,000/year, 95% CI 15.7-17.2) and 0 to 4 (10.7/100,000/year, 95% CI 10.1-11.3; p<0.0001). The highest linear increase was observed in the age groups of the 2- and 3- year-olds (12% and 13% per year, respectively for the square roots of the incidences), while the lowest increase occurred in the 11-year-olds (3% per year). Taking into consideration that the newborn population will decrease in Germany, we can expect that, in terms of absolute numbers, the highest frequency of type 1 diabetes will be among children in the 5 to 9 age group (left shift, Fig. 1).

DISCUSSION
The frequency of type 1 diabetes is rising in almost every national population (4, 5, 6). On the one hand, the considerable variation (>350-fold) in the global
incidence rates seems to be rather steady (6). On the other hand, there are differences in the incidence rates across Europe and even within various regions in an individual country, despite their close proximity and an essentially common genetic pool (4, 7). This demonstrates the interplay between genes and environment.

Our study showed that children born at the present time face a significantly higher risk of developing type 1 diabetes than those born in the 1980s and 1990s. In comparison to observations made in previous years, this risk increases further with age progression. During the last 20 years in BW there were approximately 5,100 children and adolescents who developed type 1 diabetes. Our predictions show that this figure will rise to 7,600 within the next 20 years. As immigration is not included in the population data, the predicted number of new cases might be an underestimation.

In Finland, a country with the highest IR in the world, it is estimated that the rate will reach 80/100,000/year by 2010 (8). Calculations for Germany show that a similar IR would be expected after about 50 years, i.e. in 2062. As there is a uniform pattern over the last twenty years, our calculations are based on the assumption that the incidence trend will continue also in the forthcoming years.

The question that arises in view of the rapid increase in the incidence rates among children and adolescents is whether type 1 diabetes will also be more frequent in the total population or whether the onset will occur at an earlier age (left shift). The results of the analysis of our registry point towards a left shift: during the observational period we found that the onset was most frequent among 10- to 14-year-olds; however, the average increase in the IR among 2- and 3-year-olds (+12% and +13%) is higher than the IR for 11-year-olds (+3%). Although the most distinct increase in the IR was among the 0- to 4-years-olds, our predictions show that it will be the 5- to 9-year-olds who will develop type 1 diabetes, mainly as a result of the substantial decline in the birth rate in Germany (Fig. 1). A left shift has also been observed in other countries like Belgium and Sweden (9, 10).

Based on our previous migration studies and taking into consideration the left shift in the frequency of disease occurrence, we concur with other authors that the earlier onset can be ascribed to environmental factors in individuals with a genetic predisposition (11-13). The steady and uniform rise suggests that the occurrence of type 1 diabetes can hardly be associated with short-term regional modifications, but, instead, is a consequence of lasting changes to the environment on a global scale.

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REFERENCES
