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ORIGINAL ARTICLE

# Feasibility and organization of a population-based screening for pre-symptomatic type 1 diabetes in children — evaluation of the Fr1da study

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## Abstract

**Aim** Type 1 diabetes is the most common chronic metabolic disease in childhood. Often diagnosis comes with acutely life-threatening ketoacidosis and requires hospitalization. To avoid this, early detection of children at a pre-symptomatic stage is worthwhile. This task is met by a population-based screening in Bavaria, Germany – the Fr1da study. Here, we aim to evaluate the study concept, feasibility and medical evidence of the Fr1da study.

**Methods** 308 pediatricians, 16 diabetes care centers and participating families were asked to evaluate the Fr1da study by completing questionnaires assessing study concept and feasibility, educational program and study organization. The assessment was done anonymously. In order to evaluate the effectiveness of the training the parents had to answer questionnaires to assess their knowledge about diabetes.

**Results** 48% of pediatricians and 56% of pediatric diabetes care centers filled out the questionnaire. The majority positively judged the collaboration with the Fr1da coordinating center and the feasibility to integrate the project into daily routine. Medical evidence of the screening was recognized and most of the respondents endorsed the screening to be permanently integrated into standard care-program. The majority of parents would recommend the study to other parents with young children since they were satisfied with the collaboration with pediatricians, diabetes care centers and the coordinating center. Quality control of the educational program revealed good understanding of the teaching content.

**Conclusion** The Fr1da study received high acceptance and recognition by both, health care providers and participating families, and demonstrated sustainable success with the developed educational program.

**Keywords** Public health · Children · Endocrine disorders, incl. Diabetes · Prevention

## Introduction

Type 1 diabetes is one of the most common chronic diseases of childhood with a prevalence of 0.3–0.6% (Ziegler and Nepom 2010; Ehehalt et al. 2012; International Diabetes Federation 2013; Bonifacio et al. 2017). Symptomatic disease onset is often diagnosed by blood glucose measurements at the acute life-threatening onset of the disease. Acute disease onset often requires hospitalization and occurs by severe metabolic de-compensation (Ziegler and Nepom 2010; Bonifacio et al. 2017). The management of metabolic decompensation and the adaption of the families to the disease and its treatment are major personal and financial burdens (International Diabetes Federation 2013). Symptomatic type 1 diabetes is preceded by distinct identifiable stages of pre-symptomatic beta cell autoimmunity and glucose intolerance (Ziegler et al.

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2013; Insel et al. 2015a, b). Stage 1 is defined as the presence of two or more beta cell autoantibodies with normoglycemia, and stage 2 as the presence of two or more beta cell autoantibodies with dysglycemia (glucose intolerance). Diagnosis of type 1 diabetes in an early pre-symptomatic stage can help to prevent acute disease onset, and reduce the prevalence of metabolic decompensation and associated hospitalization (Elding Larsson et al. 2011; Winkler et al. 2012). It may also open the path to population-based disease prevention.

The Fr1da study explored this concept as a model public health project in Bavaria, Germany, and introduced general population-based detection of early pre-symptomatic stages of type 1 diabetes at well child visits (U-Untersuchung) to detect a high proportion of children who will develop symptomatic type 1 diabetes (Ziegler et al. 2013; Insel et al. 2015b; Raab et al. 2016). The Fr1da study was launched in 2015. The study is directed by the Helmholtz Center Munich in cooperation with the professional association of primary care pediatricians, pediatric diabetes care centers and the ministry of health of Bavaria. After 30 months of participation, the primary care pediatricians and pediatric diabetes care centers were asked to evaluate the Fr1da study concept, assess the project feasibility, and judge the organizational infrastructure. Additionally, parents with a child diagnosed with pre-symptomatic type 1 diabetes were asked to evaluate the Fr1da study. Here we present the results of this self-evaluation. To assess the effectiveness of an educational training about pre-symptomatic type 1 diabetes, which is provided to the parents, their knowledge about type 1 diabetes was tested.

## Methods

### Fr1da study design

In the Fr1da study, children aged 2–5 years in Bavaria, Germany, are screened for the presence of multiple beta cell autoantibodies (pre-symptomatic stages of type 1 diabetes) (Raab et al. 2016). A total of 74,990 children participated in the Fr1da screening by March 2018. Screening is accomplished by primary care pediatricians or physicians. Beta cell autoantibodies are measured in capillary blood samples using the 3 Screen Islet Cell Autoantibody ELISA (RSR Ltd., Cardiff, UK) (Ziegler et al. 2016). Samples with ELISA results >97.5th centile are retested using reference radiobinding assays (Amoroso et al. 2016). A venous blood sample is obtained to confirm the autoantibody status of children with at least two positive autoantibodies against insulin, GAD, IA-2 or ZnT8. Children with confirmed positive multiple beta cell autoantibodies are diagnosed with pre-symptomatic type 1 diabetes.

These children and their parents are invited to participate in an education and counseling program and metabolic staging by oral glucose tolerance test at the local pediatric diabetes care center. Diagnosis-related depression and anxiety are assessed. Details of the study protocol have been previously published (Raab et al. 2016). The study is approved by the Ethical Committee of the Technical University, Munich, Germany (No. 70/14).

### Fr1da coordinating center

The Fr1da coordinating center at the Helmholtz Center Munich is providing information and consent material, supply material (capillary and venous blood tubes, shipping supplies), and is responsible for autoantibody diagnostics and result reporting to the primary care pediatricians as well as to the pediatric diabetes care centers. A free telephone hotline is provided to physicians and families for questions and concerns. The coordinating center reimburses to primary care pediatricians and to pediatric diabetes care centers for expenses regarding consent processes, blood draws, metabolic staging, education, and psychological assessment, respectively. With regard to families participating in the Fr1da study, the coordinating center provides each family with a study assistant who is responsible for appointments, assessment of urine and/or blood glucose monitoring at home and is the primary contact person for study and diabetes related questions.

In collaboration with the Department of Medical Psychology, Hannover Medical School, Hannover, Germany the constantly evaluation of the Fr1da study by parents is performed.

### Primary care pediatricians

Primary care pediatricians are responsible for obtaining informed consent to participate in the Fr1da study, and for collecting capillary blood into 200 μl tubes. Samples are stored in a refrigerator and returned weekly to the coordinating center. Additionally, the pediatrician instructs the family to complete a 1-page questionnaire covering demographic data, type 1 diabetes family history and environmental exposures. The pediatrician may be asked to collect a venous blood sample for confirmation of positive autoantibody measurements. If a child is diagnosed with pre-symptomatic type 1 diabetes, the pediatrician is informed (phone call and written result letter) of the diagnosis and the autoantibody status, and then informs the family.

### Pediatric diabetes care centers

Pediatric diabetes care centers are responsible for education and counselling of parents of children with pre-symptomatic type 1 diabetes. The educational program instructs the parents about urine and blood glucose monitoring, symptoms of hyperglycemia, pathogenesis of type 1 diabetes, insulin action, and normal

and pathological blood glucose levels. Additionally, they perform metabolic staging by oral glucose tolerance test (OGTT) and HbA1c to assess glucose tolerance (normal, impaired or pathological). For all children with pre-symptomatic type 1 diabetes, a monitoring plan is implemented, which includes visits to the pediatric diabetes care centers every three to six months depending on the child's glucose tolerance.

### Evaluation of participation in the Fr1da study

Primary care pediatricians and pediatric diabetes care centers were asked to evaluate the Fr1da study after 30 months of participation using a 2-page questionnaire assessing study concept, study feasibility, and study organization. It was sent via a web-based Bavarian pediatric network (PaedNetz; http://www.paednetz.de) to 308 primary care pediatricians; a second 2-page questionnaire assessing study concept, educational program, and study organization was sent to 16 pediatric diabetes care centers (supplemental material). The assessment was done anonymously. Parents of children diagnosed with pre-symptomatic type 1 diabetes were asked to evaluate their participation in the Fr1da study after receiving the diagnosis. To determine the quality of the educational program, parents were asked to attend a knowledge test immediately after the training and six and twelve months later.

## Results

### Primary care pediatricians and pediatric diabetes care centers

After screening of 63,000 children in the Fr1da study, 308 primary care pediatricians and 16 pediatric diabetes care centers were asked to participate in this evaluation. 148 (48%) primary care pediatricians and 9 (56%) pediatric diabetes care centers responded and filled out the questionnaire. For each question, five categories were possible (supplemental material).

Overall, the majority of primary care pediatricians and pediatric diabetes care centers gave a very positive judgment concerning the concept of the Fr1da screening and their participation in the project. 90% of the primary care pediatricians (Table 1; question 1) as well as 100% of pediatric diabetes care centers (Table 3; question 10) endorsed the Fr1da screening from a medical point of view. Furthermore, 84% of primary care pediatricians (Table 1; question 2) judged the screening for pre-symptomatic early stage of type 1 diabetes very/somewhat useful for families including the opportunities and burden involved. This assessment was shared by 78% of pediatric diabetes care centers (Table 3; question 1). The positive judgement of participation in the Fr1da study was reflected by the positive assessment of the collaboration with the Fr1da coordinating center. Primary care pediatricians as

**Table 1** Evaluation of Fr1da screening by primary care pediatricians

| Primary care pediatricians – all ($n = 148$) | | | | | | |
|---|---|---|---|---|---|---|
| Rating | very useful n (%) | somewhat useful n (%) | average n (%) | not particularly useful n (%) | not at all useful n (%) | no response n (%) |
| 1) How useful do you think the screening is from medical point of view? | 92 (62) | 41 (28) | 11 (7) | 3 (2) | 1 (1) | 0 |
| 2) How useful do you think the screening is for the families (opportunities and burden)? | 72 (49) | 52 (35) | 20 (14) | 2 (1) | 2 (1) | 0 |
| 3) How useful would it be to integrate the screening permanently into standard check-up program? | 57 (39) | 46 (31) | 27 (18) | 12 (8) | 2 (1) | 4 (3) |
| Rating | very good n (%) | good n (%) | satisfactory n (%) | poor n (%) | very poor n (%) | no response n (%) |
| 4) How can the screening be integrated into the routine pediatric check-ups in your practice? | 42 (28) | 60 (41) | 29 (20) | 11 (7) | 2 (1) | 4 (3) |
| 5) How would you rate the information you have received from the coordinating center about the Fr1da study? | 91 (61) | 54 (36) | 2 (1) | 0 | 0 | 1 (1) |
| 6) How would you rate the availability of the coordinating center to answer questions? | 72 (49) | 63 (43) | 7 (5) | 0 | 0 | 6 (4) |
| 7) How would you rate the service provided by the coordinating center (materials, responses)? | 99 (67) | 46 (31) | 2 (1) | 0 | 0 | 1 (1) |

**Table 3** Evaluation of Fr1da screening by pediatric diabetes care centers ($n = 9$)

| Diagnosis of type 1 diabetes at pre-symptomatic early stage vs. symptomatic stage | | | | | | |
|---|---|---|---|---|---|---|
| Rating | significantly less n (%) | somewhat less n (%) | similar n (%) | somewhat greater n (%) | much greater n (%) | no response n (%) |
| 1) How would you assess the burden on families? | 4 (45) | 3 (33) | 2 (22) | 0 | 0 | 0 |
| 2) How would you assess the amount of work you have to do to provide the initial training? | 2 (22) | 4 (45) | 3 (33) | 0 | 0 | 0 |
| 3) How would you estimate the amount of work you have to do to provide the initial treatment? | 5 (56) | 2 (22) | 0 | 2 (22) | 0 | 0 |
| 4) How would you estimate the amount of work you have to do to provide long-term care? | 2 (22) | 3 (33) | 4 (45) | 0 | 0 | 0 |
| Rating | very good n (%) | good n (%) | average n (%) | poor n (%) | very poor n (%) | no response n (%) |
| 5) How would you rate the training materials for pre-symptomatic stage type 1 diabetes? | 4 (44) | 5 (56) | 0 | 0 | 0 | 0 |
| 6) How would you rate working together with the coordinating center? | 7 (78) | 2 (22) | 0 | 0 | 0 | 0 |
| 7) How would you rate the availability of the coordinating center to answer questions? | 6 (67) | 3 (33) | 0 | 0 | 0 | 0 |
| 8) How would you rate the information you have received from the coordinating center about the Fr1da study? | 6 (67) | 3 (33) | 0 | 0 | 0 | 0 |
| 9) How would you rate the current support provided by the coordinating center for children with pre-symptomatic stage T1D? | 5 (56) | 3 (33) | 1 (11) | 0 | 0 | 0 |
| 10) How would you rate the Fr1da screening from a medical point of view? | 5 (56) | 4 (44) | 0 | 0 | 0 | 0 |

well as pediatric diabetes care centers were satisfied with the information they received about the Fr1da study, the availability of the coordinating center to answer questions and the service provided by the coordinating center concerning materials and responses (Table 2; question 8–11 and Table 3; question 5–8). This well attuned working together led to very good/good possibility to integrate the Fr1da screening into daily routine for 69% of primary care physicians (Table 1; question 4). The majority of pediatric diabetes care centers, which were responsible for initial training and metabolic staging of children diagnosed with pre-symptomatic type 1 diabetes rated the amount of work concerning initial training, treatment and long-term care less than for children diagnosed at a symptomatic stage (Table 3; question 2–4). Overall, according to 70% of primary care pediatricians (Table 1; question 3) it would be very/somewhat useful to integrate the screening for pre-symptomatic type 1 diabetes permanently into the standard screening and check-up program.

## Parents

258 parents of 129 children diagnosed with a pre-symptomatic stage of type 1 diabetes were asked to evaluate the Fr1da study six months after receiving the diagnosis. 170 (66%) parents responded and filled out the 6 months questionnaire. For each question, five categories of appreciation were given.

Overall, the participating parents gave a positive judgement concerning their decision to participate in the Fr1da study. 84% of parents (Fig. 1, Suppl. Table 1, question 1) were very satisfied/ satisfied that their child is participating in the Fr1da study. 145 (85%) parents were very satisfied/satisfied with the communication of the diagnosis of a pre-symptomatic stage of type 1 diabetes by their primary care pediatrician (Fig. 1, Suppl. Table 1, question 5). The educational training provided by pediatric diabetes care centers was also mostly positively judged (Fig. 1, Suppl. Table 1, question 6). The majority of parents were also satisfied with the support they received from the coordinating center. This included the opportunity to contact someone with questions (Fig. 1, Suppl. Table 1, question 7), the organization of the Fr1da study (Fig. 1, Suppl. Table 1, question 8) and the written information provided (Fig. 1, Suppl. Table 1, question 9). Altogether, 80% of parents at six months (Suppl. Table 1, question 2) assessed their decision to participate in the Fr1da study as very good/good.

To determine the effectiveness of the educational training, parents were asked to answer questions about type 1 diabetes immediately after the training and six and twelve months later (Fig. 2). 157 (55%) parents participated the test immediately after the training, 156 (60%) parents after six months and 114 (62%) parents after twelve months. 80 to 90% of parents could list at least three symptoms of acute hyperglycemia in children (Suppl. Table 2, questions 1) initially, six and twelve months after the training.

The knowledge about blood sugar values fasting and after a meal (Suppl. Table 2, questions 2 and 3) increased during the time of participation. Parents were introduced to blood sugar measurements at their follow-up visits, especially if children changed from normal to impaired glucose tolerance. For children with normal glucose tolerance, urine glucose measurements were recommended once a month. 50 to 60% of parents knew which color indicated elevated glucose in the urine using urine testing stix (Suppl. Table 2, question 4).

## Discussion

The Fr1da study is one of the largest public health research studies in diabetes engaging children and families, their primary care pediatricians, as well as diabetes clinical care centers under leadership of one central coordination center and laboratory. Until evaluation, over 63,000 families participated through their primary care physicians in the Fr1da study

**Table 2** Evaluation of Fr1da screening by primary care pediatricians with at least one child diagnosed with pre-symptomatic type 1 diabetes

| Primary care pediatricians – with at least one child diagnosed with pre-symptomatic type 1 diabetes ($n = 49$) | | | | | | |
|---|---|---|---|---|---|---|
| Rating | very good n (%) | good n (%) | satisfactory n (%) | poor n (%) | very poor n (%) | no response n (%) |
| 8) How would you rate the information on diagnosis provided by the coordinating center? | 25 (51) | 16 (33) | 5 (10) | 3 (6) | 0 | 0 |
| 9) How would you rate the referral of the family to a pediatric diabetes care center for training and consultation? | 21 (43) | 15 (31) | 7 (14) | 2 (4) | 0 | 4 (8) |
| 10) How would you rate the support provided by the coordinating center for the ongoing care of the family and the child? | 24 (49) | 12 (24) | 6 (12) | 4 (8) | 0 | 3 (6) |
| 11) How would you rate the current support provided by the pediatric diabetes care center for the family and the child? | 22 (45) | 18 (37) | 4 (8) | 1 (2) | 0 | 4 (8) |

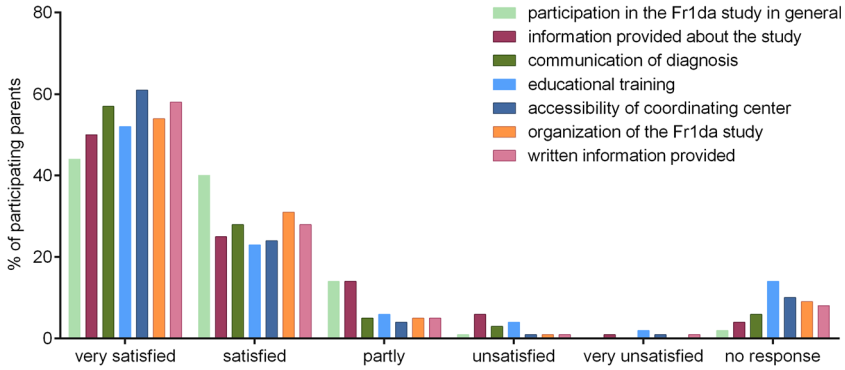


**Fig. 1** Evaluation of Fr1da study by participating families six months after educational training ($n = 170$). The parents were asked about their satisfaction of different study aspects, the percentage of each rating is plotted

indicating that the Fr1da study concept was well accepted in the population and medical community. As we think it is important to quantify the benefits of research in society early in our project to be able to adjust our approach in case of suboptimal results we asked participating primary care providers and specialists as well as parents to evaluate the Fr1da public health project after 30 months of implementation/operation.

The overall feedback was positive. In summary, the preliminary evaluation demonstrated that the public health Fr1da project reached the medical community and was well perceived from primary care providers and specialists. The implementation into daily routine was mostly considered feasible. The societal impact of an early diagnosis of type 1 diabetes was recognized. The central organization was acknowledged. The strength of our evaluation was that two different professional groups as well as the patients were included into the evaluation, and that the project was operating for a long enough period before the evaluation was performed. The limitations included the participation rate of less than 50%.

Several surveys reflecting the motivation of physicians for research participation revealed that to facilitate physician participation, the research topic should be in-line with their interest, relevant and important to their field, linked to the real

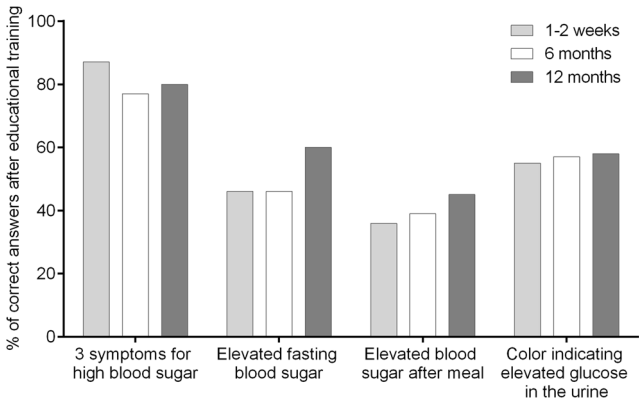


**Fig. 2** Assessment of effectiveness of the educational training. Parents were asked diabetes related questions one to two weeks ($n = 157$), six ($n = 156$) and twelve ($n = 114$) months after the educational training, the percentage of correct answers is plotted for each question

world of clinical practice, and above all, should have clear potential to improve patient care (Albers and Sedler 2004; Armstrong et al. 2009; Duca et al. 2017). It is mentioned that activities integrated into the usual patterns of patient care which do not interfere with the flow of patient care increase the likelihood of physician participation (Armstrong et al. 2009). Regular feedback and support along with financial compensation as it is practiced in the Fr1da study will motivate physicians to participate in clinical research (Yanos and Ziedonis 2006; Rahman et al. 2011).

Patient satisfaction is an increasingly important measure in health care delivery. Studies have demonstrated positive associations between overall patient satisfaction and clinical outcomes (Glickman et al. 2010). It has been shown that patient satisfaction correlates highly with communication with nurses and/or certified clinical research coordinators/assistants, who represent the larger organization (Manary et al. 2013). In terms of the Fr1da study this is reflected by the overall positive judgement of the organization and care provided by primary care pediatricians, pediatric diabetes expert centers and the coordinating center. This leads to a general satisfaction with the participation in the study. In addition, most parents were satisfied with their decision to participate in the Fr1da screening, which indicates an acceptance of the Fr1da concept although personal interviews with the families have shown that the diagnosis of pre-symptomatic stage type 1 diabetes came unexpectedly for most parents.

We conclude that the Fr1da study works so well because primary care physicians, pediatric diabetes care centers and families were well integrated into the whole concept of the study and the medical community was convinced of a potential improvement of patient care.

As the educational training and medical care has been implemented at multiple locations, a process evaluation is essential to ensure that the planned interventions are carried out equally at all sites. Since our analysis demonstrated that the majority of parents had a sustainable knowledge about important aspects of type 1 diabetes care and potential complications we assess the output of the educational training positively. This could prevent severe metabolic decompensation.

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## Compliance with ethical standards

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Conflict of interest** The authors declare that they have no conflict of interest.



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