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The emotional well-being of parents with children at genetic risk for type 1 diabetes before and during participation in the POInT-study

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Abstract

This study examined the emotional impact that parents experience when confronted with an increased genetic risk of type 1 diabetes (T1D) in their child. Population-based screening of neonates for genetic risk of chronic disease carries the risk of increased emotional burden for parents.

Information was collected using a well-being questionnaire for parents of infants identified as having an increased risk for T1D in a multinational research study. Parents were asked to complete this questionnaire after they were told their child had an increased risk for T1D (Freder1k-study) and at several timepoints during an intervention study (POInT-study), where oral insulin was administered daily.

Data were collected from 2595 parents of 1371 children across five countries. Disease-specific anxiety was found in a larger group of parents (47.2%) during the intervention study. Panic-related anxiety symptoms were reported by only 4.9% after hearing about their child having an increased risk. Symptoms of depression were limited to 19.4% of the parents at the result-communication visit and declined over time during the intervention study. Mothers and parents with a first-degree relative (FDR) with T1D reported more symptoms of depression and disease-specific anxiety ($p < 0.001$) than fathers and parents without a FDR.

Overall, symptoms of depression and panic-related anxiety are comparable with the German general population. However, high levels of disease-specific anxiety were found during the intervention study, which should be kept in mind when considering population-based screening. As certain subgroups are more prone, it will be important to continue psychological screening and, when necessary, to provide support by an experienced, multidisciplinary team.

Keywords: type 1 diabetes, genetic risk, parents, emotional well-being, prevention

Introduction

Type 1 diabetes (T1D) is the most common metabolic disease encountered during childhood and the incidence is rising worldwide[1]. In Europe, the incidence of T1D is 15 per 100.000 people, with a prevalence of 12,2 per 10.000 people[2]. The natural course of T1D consists of three stages. The first stage is characterized by the presence of two or more autoantibodies without clinical signs. In the second stage, the reserve of pancreatic β -cells decreases, resulting in abnormal glucose tolerance, and in the third stage the patient becomes symptomatic[3]. The treatment of T1D is based on the administration of exogenous insulin. Although the astounding progress in contemporary therapy of T1D has a positive impact on general health and quality of life[4], patients with symptomatic T1D must deal with multiple challenges, such as blood glucose fluctuations with hypo- or hyperglycemia[3], a combination of administering basal and bolus insulin, monitoring blood glucose levels, and considering the relationship between insulin, blood glucose levels, activity and food, especially by counting carbohydrates[5]. Short-term complications of T1D include hypoglycemia and diabetic ketoacidosis, while long-term complications such as retinopathy, nephropathy and neuropathy can develop after years[6]. An important determining factor for survival is the age at onset of the disease[7].

Prevention is key because there is no cure for T1D. Within the context of T1D, there are three types of prevention: primary, secondary, and tertiary. The goal of primary prevention is to inhibit the production of antibodies against the β -cells[8] and to halt the development of stage 1 diabetes[9] and therefore focuses on the intervention when the autoimmune attack has not yet started. To explore the possibility of primary prevention of T1D, the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) was established in 2015. GPPAD was created to allow a multidisciplinary approach to prevent T1D.

The first step in developing a prevention strategy is to identify children who are at risk and include them in prevention trials. The GPPAD-02 study (also known as the Freder1K-study) screens newborns to identify a >10% risk for developing multiple beta-cell autoantibodies by the age of 5 years using 46 T1D susceptibility single-nucleotide polymorphisms (SNPs) or three SNPs and a first-degree family history for T1D[1]. Genetic testing is performed before the age of 5 months in a large cohort of newborns spread across Germany, the

United Kingdom, Poland, Belgium and Sweden[1]. Infants with an increased risk were included in the POInT-study (also known as the GPPAD-03 study), a multicenter primary prevention trial, which started in February 2018[10]. The objective of this randomized controlled trial is to determine whether daily administration of oral insulin has an influence on the initiation of beta-cell autoimmunity and the onset of T1D.

With current scientific advances, genetic testing is becoming more common. Therefore, it is important to identify the overall impact of these techniques. When parents are confronted with their child's increased genetic risk of a chronic disease, this can provoke feelings of depression or anxiety[11,12]. For most parents the anxious feelings are common reactions to this sudden knowledge and reduce quickly over time[11]. The GPPAD-02 pilot study in Saxony did not demonstrate signs of excessive burden[13], however certain subgroups of parents might be more susceptible to levels of depression and anxiety[11,14].

This study aims to broaden the knowledge of the emotional impact on parents confronted with their child's increased genetic risk of T1D. Symptoms of depression and anxiety and the burden on parents were examined after hearing about the high risk for T1D in their child and at different timepoints during the POInT-intervention-study. Research on possible independent variables of anxiety and depression in this context may lead to better understanding and psychological support in the future. The aim is to explore potential differences in levels of depression and anxiety between mothers and fathers, between parents with or without a first-degree relative suffering from T1D and between the participating countries as well as exploring the emotional impact on parents over time.

Methods

This study was organized by GPPAD, a network of collaborating investigators from eight clinical trial centers located in five European countries: Germany (Munich, Hannover, Dresden), the UK (Oxford), Poland (Warsaw), Belgium (Leuven), and Sweden (Malmö and Kristianstad). This study is part of the GPPAD-02-study and the POInT-study, conducted by the GPPAD group. Data were collected from the eight GPPAD clinical trial centers located in five European countries (Addendum I).

After participating in the GPPAD-02-study, both parents and/or guardians of at-risk children were contacted by telephone by an experienced physician/nurse from the local team. The family was informed about the increased predisposition and invited to a consultation (= information visit or result-communication visit), or alternatively a videoconference or phone call. This visit, preferably with all (custodial) parents, ideally took place before the age of 5 months. During this visit, a qualified physician provided information to the parents about their child being at high risk for T1D and about T1D itself. Parents' questions and concerns were addressed. Afterwards, the objectives of the POInT-study were explained[1]. Parents were asked to complete a well-being questionnaire (= T1) that screens for symptoms of depression and anxiety. During the COVID-19 pandemic, some of the visits took place online. Parents who decided to participate in the POInT-study were asked to fill in a well-being questionnaire during follow-up study visits 4 months after enrollment into POInT-Study (T2), when the child was 18 months old (T3) and when the child was 36 months old (T4) (Figure 1).

The well-being questionnaire consists of three parts (Addendum II). The first part contains 9 questions, which is based on the Patient Health Questionnaire (PHQ-9). These are short and simple questions regarding problems with mood, worry, sleep, appetite and concentration. There are four response options: not at all (0), several days (1), more than half the days (2) and nearly every day (3). A depression total score (DTS) is calculated: the sum of PHQ1 – PHQ 9 with a minimum of 0 and a maximum of 27. DTS can be categorized as following: 0 = no symptoms (0-4); 1 = mild symptoms (5-9); 2 = moderate symptoms (10-14); 3 = moderately severe symptoms (15-19); 4 = severe symptoms (20-27). It is known from previous research[15] that when used for screening, the pooled sensitivity and specificity for PHQ-9 are 0.77 and 0.85,

respectively, meaning the PHQ-9 has a limited sensitivity however a good specificity. The second part of the questionnaire consists of five yes (1)-or-no (0) questions about the occurrence and experience of anxiety attacks, derived from the PHQ-D series. Anxiety total score (ATS) can be measured by the sum of these five questions. If a parent answers 'no' to the first question, regarding the presence of anxiety attacks, the other four questions are not completed, as all answers from anxiety question 2 (AQ2) until anxiety question 5 (AQ5) are considered 'no'. Therefore, these items are considered as the panic-specific anxiety symptoms. The third section differs in the first questionnaire (GPPAD-02-study) compared to the questionnaire during the follow-up visits (3, 5 and 8) in the intervention study. In the first questionnaire three additional multiple-choice questions that probe the overall experience during the study are added: impact on daily life, expectation of increased risk and strain on mental health. The third section of the follow-up questionnaire during the POInT-study consists of six additional multiple-choice questions, exploring impact on daily life, worrying about the child developing T1D, feelings when thinking about the child developing T1D, feelings about participation and their decision to participate in the POInT-study and a question about whether to recommend the study to other parents. Feelings when thinking about the child developing T1D are considered as diseased-specific symptoms of anxiety. These questions are derived from the State Anxiety Inventory (SAI)[14,16], a shortened questionnaire with six items from the State-Trait Anxiety Inventory (STAI) and measure feelings of tension, anxiety and nervousness. As in previous studies, a score of > 40 adapted for the SAI is indicative of high disease-specific anxiety.

When a parent was diagnosed with elevated levels of anxiety and/or distress, a structured assessment of the burden and need for support was carried out (Addendum III). Thereafter, if the psychological burden was a consequence of study participation, a psychologist offered a specialized approach in caring for families with newly diagnosed children with T1D. This included personal counseling focused on diabetes-specific anxiety and guilt, elements of cognitive behavioral therapy focused on negative thoughts, support with diabetes-specific parenting, family counseling and referral to psychotherapy when needed.

For the statistical analyses SPSS version 28.0.0.0. was used. Means were used to determine the levels of depression and anxiety symptoms in different groups. To test normality, the Kolmogorov-Smirnov test was applied. One-way ANOVA tests were used if the data were parametric. If not, Mann-Whitney U and Kruskal-Wallis tests were utilized. Proportions were compared using Pearson's chi- squared test. For the longitudinal analyses, repeated measures (ImerTest Package in R, version 4.2) and paired sample t-test were used. Associations were considered statistically significant when the p-value was <0.05.

Results

All completed questionnaires (5730) between November 2017 and May 2022 were processed from the GPPAD reports and used in this study. Data were collected from 2595 parents of 1371 children. The group of parents included 1331 women (51.3%) and 1148 (44.2%) men. Gender was not mentioned by 116 parents (4.5%). The distribution among the different countries was as follows: 688 children (50.1%) from Germany (München, Hannover and Dresden), 195 (14.2%) from Sweden (Malmö and Kristianstad), 87 (6.3%) from Belgium (Leuven), 353 (25.7%) from Poland (Warsaw), and 49 (3.6%) from the UK (Oxford). Of all participants, 721 (52.6%) did not have a first degree relative with type 1 diabetes, the remaining 650 (47,4%) reported having at least one (table 1).

No symptoms of depression (DTS ≤ 4) were reported by 80.6% of the parents at the first visit (T1 = result communication visit) when the results of an increased genetic risk of T1D were communicated; 86.2% at T2, 88.2% at T3 and 87.2% at T4, while mild, moderate, moderate-severe and severe symptoms (DTS > 4) were reported by 19.4% at T1, 13.9% at T2, 11.9% at T3 and 12.8% at T4 (table 2; figure 2). No anxiety symptoms (panic-specific) were reported by 92.9% at T1, 94.7% at T2, 96.1% at T3 and 95.2% at T4, while one or more anxiety symptom(s) were reported by 4.9% at T1, 4.4% at T2, 3.2% at T3 and 3.7% at T4 (table 3: figure 3). When comparing DTS at different times, a higher score was found for visit 1 compared to visit 3, 5 and 8 ($p < 0.001$). For ATS, a significant difference was found between T1 and T3 ($p = 0.046$), however not for T1 and T2/T4. Regarding disease-specific anxiety symptoms, 44.8% reported to experience low disease-specific anxiety, while 47.2% reported high disease-specific anxiety.

Gender of parent

Regarding gender of the parent, significantly higher levels were found for both DTS and ATS in mothers compared to fathers at all timepoints (table 4; figure 4 and 5). The evolution over time differed between mothers and fathers for DTS ($p < 0.001$) and ATS ($p < 0.001$) (figure 6 and 7). During the result communication visit, mothers reported more emotional distress than fathers ($p < 0.001$; men: 11.2% & women: 20.9%). Furthermore, in the group of mothers, 23.3% scored above 4 (> mild symptoms) on the

DTS, which differed significantly ($p < 0.001$) from the father's group, which was only 14.6%. When looking at disease-specific anxiety during the PoINT-study, mothers worried more that their child would get diabetes ($p < 0.001$) and, when thinking of the child's risk, reported to feel less calm ($p < 0.001$), relaxed ($p < 0.001$) and at-ease ($p < 0.001$) and more worried ($p < 0.001$), tense ($p < 0.001$) and nervous ($p < 0.001$) than fathers. In total, mothers reported more disease-specific anxiety than fathers ($p < 0.001$). High disease-specific anxiety was reported by 53.7% of the mothers, compared to 39.3% in the group of fathers.

First degree relative

When looking at differences in depression and anxiety symptoms in parents with or without a first-degree relative (FDR), a significantly higher score for self-reported depression symptoms was found in the group with a first-degree family history at T1, however not at the follow-up visits (table 5). The anxiety scores were not significantly different (table 5). A significant difference in evolution over time was found between having or not having a first-degree relative for DTS ($p = 0.018$), but not for ATS ($p = 0.781$) (figure 8 and 9).

A key finding is that parents with a positive family history were more likely to expect a positive test result ($p < 0.001$; No FDR: 12.4% & FDR: 65.3%). At T1, the group of parents with a first-degree relative reported significantly more emotional distress than the group of parents without a first-degree relative with T1D ($p < 0.001$; No FDR: 12.7% & FDR: 20.4%). It was noted that 12.4% of parents without a first-degree relative also expected a positive result. Within this group of parents without a positive family history, a significant positive association was found between expecting a positive result and experiencing emotional distress ($p = 0.005$).

When looking at disease-specific anxiety during the PoINT-study, participants with a first-degree relative worried more that their child would get diabetes ($p < 0.001$) and, when thinking of the child's risk, reported to feel less calm ($p < 0.001$), relaxed ($p < 0.001$) and at-ease ($p < 0.001$) and more worried ($p < 0.001$), tense ($p = 0.006$) and nervous ($p = 0.002$) than participants without a FDR. In total, parents with a first-degree relative reported more disease-specific anxiety than parents without a first-degree relative ($p < 0.001$). High disease-specific anxiety was reported by 51.5% of parents with a first-degree relative, compared to 42.0% without a first-degree relative.

Country

Regarding country, a significant difference in levels of DTS and ATS was found between the countries at all four times (table 6). During the result-communication visit (T1), analysis of the DTS showed a significantly higher score among participants in Poland compared to participants in Germany ($p < 0.001$) and Sweden ($p = 0.018$). Analysis of the ATS showed a lower score among participants in Germany compared to Sweden ($p < 0.001$) and Belgium ($p = 0.005$). During T2, participants of Germany reported lower DTS and ATS than participants of Sweden ($p < 0.001$; $p < 0.001$), Belgium ($p < 0.001$; $p < 0.001$), Poland ($p < 0.001$; $p < 0.001$) and the UK ($p = 0.038$; $p < 0.001$). Participants of Poland reported more DTS than participants of Sweden ($p = 0.004$), Belgium ($p = 0.013$) and the UK ($p = 0.036$). During T3, participants in Germany reported significantly lower symptoms of depression and anxiety than participants in Sweden ($p < 0.001$; $p < 0.001$), Belgium ($p < 0.001$; $p < 0.001$), Poland ($p < 0.001$; $p < 0.001$) and the UK ($p = 0.010$; $p = 0.002$). Finally, during T4, depression and anxiety total scores were both significantly higher in Poland than in Germany ($p < 0.001$; $p < 0.001$). Regarding DTS, participants in Sweden reported higher scores than in Germany ($p = 0.046$).

Expectation of a positive result during the result-communication visit

During the result-communication visit in the group of parents who expected a positive test result, 23.0% scored above 4 on the DTS (having at least mild symptoms). In the group that did not expect a positive test result, this was only 16.8% ($p = 0.002$).

Feelings of participation during the POInT-study

When asking about their feelings about participating in the POInT-study, 97.2% reported they thought it was ok or liked it (a lot), 98.9% reported that they thought it was an ok or a (very) good decision and 89.7% would recommend the study to others.

Discussion

In the absence of a cure, prevention of T1D is key. Therefore, neonatal screening for genetic risk and preventive therapy might be important steps in this process. Detecting an increased genetic risk may be a medical advantage but only if this outweighs the emotional impact on parents. When parents are confronted with their child's increased genetic risk of a chronic disease, this can provoke feelings of anxiety or depression[11,12]. For most parents the anxious feelings are common reactions to this sudden knowledge and reduce over time[11].

Studying the impact on the emotional well-being of these parents in depth is important. To our knowledge, this is the first study with a large, multinational cohort to investigate the psychological impact on parents when hearing about an increased genetic risk for T1D in their child and subsequently over time during their participation in an intervention study.

This study shows that symptoms of depression and panic-specific anxiety are similar compared to the German general population [17,18], which is in line with the Freder1k-pilot-study in Saxony that did not demonstrate signs of excessive burden[13]. Almost half of the participating parents reported to have high disease-specific anxiety. During the intervention study, symptoms of depression declined, however this decline was not found for symptoms of anxiety.

In line with the literature, this study finds that mothers are experiencing more symptoms of depression and anxiety. Consistent with studies by Johnson S.B. (et. al.)[11,14], mothers are feeling more anxious, both panic- as well as disease-specific. The Environmental Determinants of Diabetes in the Young or TEDDY study[19], a large, prospective cohort study, found that maternal anxiety is raised when their child is at increased risk. In the general population, the mean PHQ-9 score in women is also significantly higher than in men[18] and similarly, both depression and anxiety levels in parents of children with chronic illnesses are higher in mothers compared to fathers[20]. The presented feelings of depression and anxiety may be enhanced by personal factors, such as coping styles[11], which could be an interesting starting point for future research.

Furthermore, this study demonstrates that parents with a family history of T1D experience more depressive symptoms and report more emotional distress than parents without a family history when the result of an increased genetic risk is communicated. They are also more likely to expect a positive genetic test result. Previous studies found that anxiety levels are higher in families with a first-degree relative with T1D[11,14], which in this study is confirmed for disease-specific anxiety, however not for panic-specific anxiety. A possible explanation could be the structure of the panic-specific anxiety items in the questionnaire. When parents reported to have no anxiety attack or suddenly feeling fear or panic, other questions were no longer included, and this was seen as reporting no symptoms of anxiety. Unfortunately, this threshold might be too high, as there are many other symptoms of anxiety, such as feeling nervous/anxious, not being able to stop worrying, having trouble relaxing and being irritable. In future research, it might be useful to screen for symptoms of anxiety in general with the General Anxiety Disorder – 7 (GAD-7)[21]. Interestingly, there are many children with a first-degree relative with T1D participating in this study, possibly meaning that these parents are particularly concerned and/or that they are more likely to support diabetes research through their participation.

Finally, symptoms of depression and anxiety are compared in the five participating countries. Some important caveats must be considered. Firstly, the groups were unevenly distributed, with the largest group in Germany and the smallest group in the UK. Secondly, only German studies generated a baseline for the general German population, however not specifically for parents of young children[17,18]. This resulted in comparable results to our study: a mean score of 3.1 (S.D. ± 3.5) for women and 2.7 (S.D. ± 3.5) in men (12) for symptoms of depression and about 6.0% reported to have had a panic attack in the last four weeks. In the absence of data in the general population from the other participating countries (Belgium, Sweden, Poland, and the UK), a reliable comparison is difficult. Thirdly, there is no standardized way to compare the approach in the different centers and countries. There are general agreements about the procedure, but no certainty about its implementation. With the available information, it is not possible to determine whether the differences are due to a difference in population or to a difference in approach, such as empathy, communication, information, structured education, access to individual team members, structured psychological care and commitment.

Important to note is that levels of symptoms of depression and anxiety in most cases are still acceptable. It would be valuable to be able to predict who is emotionally more at risk, such as women and parents with a FDR with T1D, to prevent a high impact on their emotional well-being and therefore, further research is necessary. Johnson et al. (2017)[14] found that anxiety in parents of children with two or more

types of autoantibodies was particularly high, while it declined to normal levels in response to repeated negative autoantibodies. Furthermore, outliers were often seen in parents with known psychological problems. Providing support for these parents by an experienced, multidisciplinary team is important.

The TEDDY study shows that, despite medical advice to the contrary, lifestyle modifications are made in 42% of families with a child with an increased genetic risk in an effort to stop the development of T1D[19]. This preventive behavior can possibly be explained by underlying anxious feelings[14] and can influence study outcomes in longitudinal prevention studies[11]. These non-evidence-based behavioral changes were also noted in other studies[12] and may be potentially harmful to the emotional well-being of the parents and the child.

The fact that genetic testing for T1D only implies a risk of 1 in 10 and therefore no certainty, might be difficult to handle[12]. Compared to other neonatal screening tests, this genetic test does not lead to a definitive diagnosis. That is why N. J. Kerruish[12] describes this as a dilemma between preparing oneself for a disease that may never come or ignoring the genetic risk and missing out on the opportunity for such preparation. Uncertainty about the future occurrence of the disease might create confusion. Since every individual is different and because of the ambiguity inherent to the genetic testing, the emotional response differs from parent to parent[12]. A similar problem exists in the context of cystic fibrosis (CF). For 45 years, newborns with CF have been detected by the heel prick test resulting in faster follow-up and better treatment[22]. However, there is a flip side of the coin. As the genetic testing continues to expand, a group of children is encountered with a genetic disorder but no current metabolic disease[22]. In Europe, this group is called “CF-screen positive, inconclusive diagnosis” or CFSPID. These are symptom-free children of whom only a small proportion will later develop CF[22]. Qualitative research in this domain suggests that there is a significant negative impact on the psychological well-being of these families[23]. An important factor is the uncertainty and ambiguity associated with this diagnosis.

An argument for this screening is that research has shown that unexpected traumatic events, such as a sudden diagnosis of T1D or diabetic ketoacidosis, cause more psychological harm than expected or predicted events, such as a diagnosis after a positive screening result[24]. Hence, it must be considered that study participation and genetic testing in general may be emotionally beneficial to families where the child eventually develops diabetes. In these cases, genetic information can help families to be better prepared both emotionally and practically[12]. Nevertheless, most of the participating children will not develop T1D and for this group, the increased genetic risk may be considered a "false alarm". Research in the CF-area

has taught us that prompt, clear and accurate information, and communication is necessary to minimize the psychological impact[23]. It can also help to point parents to correct sources of information.

Finally, it is important to mention that the decision about genetic testing and study participation is made by the parents. An ethical concern with neonatal screening is the elimination of the child's choice. Later in life, the child might not want to know his/her genetic status[12]. Follow-up data should be collected, and the long-term psychological effect must be investigated in these children.

Conclusion

The goal of the GPPAD group is primary prevention of this disease. The first step in this process is to identify infants at increased genetic risk by the GPPAD-02-study. It should be considered that the ambiguity of the increased risk might have an impact on the emotional well-being of these families. Overall, symptoms of depression and panic-specific anxiety are comparable with the general population. However, higher levels of disease-specific anxiety were found during the intervention study. Specific risk factors should be kept in mind: mothers and parents with a first-degree relative experience more symptoms of depression and anxiety and emotional distress compared to fathers and parents without a first-degree relative. Furthermore, one of the next challenges and possible risk factor is the diagnosis of two or more autoantibodies, reflecting the development of the disease in the next few years. In the future it will therefore be important to continue psychological screening and, when necessary, provide support by an experienced, multidisciplinary team for these families over time.

References

1. Winkler C, Haupt F, Heigermoser M, et al. Identification of infants with increased type 1 diabetes genetic risk for enrollment into Primary Prevention Trials—GPPAD-02 study design and first results. *Pediatr Diabetes*. 2019;20(6):720-727. doi:10.1111/pedi.12870
2. Mobasseri M, Shirmohammadi M, Amiri T, Vahed N, Fard HH, Ghojazadeh M. Prevalence and incidence of type 1 diabetes in the world: A systematic review and meta-analysis. *Health Promot Perspect*. 2020;10(2):98-115. doi:10.34172/hpp.2020.18
3. Dayan CM, Korah M, Tatovic D, Bundy BN, Herold KC. Changing the landscape for type 1 diabetes: the first step to prevention. *The Lancet*. 2019;394(10205):1286-1296. doi:10.1016/S0140-6736(19)32127-0
4. Misso ML, Egberts KJ, Page M, O'Conner D, Shaw. J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane database of systematic reviews*. 2010;1.
5. Stephens E. Insulin Therapy in Type 1 Diabetes. *Medical Clinics of North America*. 2015;99(1):145-156. doi:10.1016/j.mcna.2014.08.016
6. Rochtus A, Casteels K. Actuele aanpak diabetes type 1 bij kinderen. *Vlaams Tijdschrift voor Diabetologie*. 2020;1:26-28.
7. Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *The Lancet*. 2018;392(10146):477-486. doi:10.1016/S0140-6736(18)31506-X
8. Primavera M, Giannini C, Chiarelli F. Prediction and Prevention of Type 1 Diabetes. *Front Endocrinol (Lausanne)*. 2020;11(June):1-9. doi:10.3389/fendo.2020.00248
9. Haller MJ, Atkinson MA, Schatz D. Type 1 diabetes mellitus: Etiology, presentation, and management. *Pediatr Clin North Am*. 2005;52(6):1553-1578. doi:10.1016/j.pcl.2005.07.006
10. Ziegler AG, Achenbach P, Berner R, et al. Oral insulin therapy for primary prevention of type 1 diabetes in infants with high genetic risk: The GPPAD-POInT (global platform for the prevention of autoimmune diabetes primary oral insulin trial) study protocol. *BMJ Open*. 2019;9(6). doi:10.1136/bmjopen-2018-028578
11. Johnson SB. Psychological impact of screening and prediction in type 1 diabetes. *Curr Diab Rep*. 2011;11(5):454-459. doi:10.1007/s11892-011-0208-9
12. Kerruish NJ. Parents' experiences of newborn screening for genetic susceptibility to type 1 diabetes. *J Med Ethics*. 2011;37(6):348-353. doi:10.1136/jme.2010.039206

13. Hommel A, Haupt F, Delivani P, et al. Screening for Type 1 Diabetes Risk in Newborns: The Freder1k Pilot Study in Saxony. *Hormone and Metabolic Research*. 2018;50(1):44-49. doi:10.1055/s-0043-120921

14. Johnson SB, Lynch KF, Roth R, Schatz D, and the TEDDY Study Group. My child is islet autoantibody positive: Impact on parental anxiety. *Diabetes Care*. 2017;40(9):1167-1172. doi:10.2337/dc17-0166

15. Manea L, Gilbody S, McMillan D. A diagnostic meta-analysis of the Patient Health Questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression. *Gen Hosp Psychiatry*. 2015;37(1):67-75. doi:10.1016/j.genhosppsych.2014.09.009

16. Spielberger C, Gorsuch R, Lushene R. Test Manual for the State-Trait Anxiety Inventory. *Palo Alto, CA, Consulting Psychologists Press, 1970*.

17. Rief W, Nanke A, Klaiberg A, Braehler E. Base rates for panic and depression according to the Brief Patient Health Questionnaire: A population-based study. *J Affect Disord*. 2004;82(2):271-276. doi:10.1016/j.jad.2003.11.006

18. Kocalevent RD, Hinz A, Brähler E. Standardization of the depression screener Patient Health Questionnaire (PHQ-9) in the general population. *Gen Hosp Psychiatry*. 2013;35(5):551-555. doi:10.1016/j.genhosppsych.2013.04.006

19. Smith LB, Lynch KF, Baxter J, et al. Factors associated with maternal-reported actions to prevent type 1 diabetes in the first year of the TEDDY study. *Diabetes Care*. 2014;37(2):325-331. doi:10.2337/dc13-0449

20. van Oers HA, Haverman L, Limperg PF, van Dijk-Lokkart EM, Maurice-Stam H, Grootenhuis MA. Anxiety and Depression in Mothers and Fathers of a Chronically Ill Child. *Matern Child Health J*. 2014;18(8):1993-2002. doi:10.1007/s10995-014-1445-8

21. Spitzer R, Kroenke K, Williams J, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097.

22. Barben J, Southern KW. Cystic fibrosis screen positive, inconclusive diagnosis. *Curr Opin Pulm Med*. 2016;22(6):617-622. doi:10.1097/MCP.0000000000000314

23. Johnson F, Southern KW, Ulph F. Psychological impact on parents of an inconclusive diagnosis following newborn bloodspot screening for cystic fibrosis: A qualitative study. *Int J Neonatal Screen*. 2019;5(2). doi:10.3390/ijns5020023

24. Smith LB, Liu X, Johnson SB, et al. Family adjustment to diabetes diagnosis in children: Can participation in a study on type 1 diabetes genetic risk be helpful? *Pediatr Diabetes*. 2018;19(5):1025-1033. doi:10.1111/pedi.12674

Tables:

Table 1: Descriptive Table of Study Population: N per timepoint and percentages per timepoint per country/for mothers vs. fathers and having vs. not having a first-degree relative

	T1	T2	T3	T4
N	1741	1722	1561	602
Country				
- Germany	61.5%	53.7%	55.7%	61.5%
- Sweden	14.8%	13.4%	11.7%	9.1%
- Belgium	8.5%	8.5%	9.0%	2.0%
- Poland	15.2%	19.6%	19.3%	21.6%
- UK	/	4.8%	4.3%	5.8%
Gender parent				
- Male	46.2%	43.8%	44.5%	44.9%
- Female	53.4%	55.7%	55.2%	55.1%
First degree family history				
- No	52.8%	45.5%	46.7%	37.9%
- Yes	47.2%	54.5%	53.3%	62.1%

§ In the UK, the emotional well-being questionnaire was not yet administered during the GPPAD-02 study, therefore explaining the absence of data.

Table 2: Frequencies, mean and standard deviation (SD) of symptoms of depression per timepoint

	T1	T2	T3	T4
No symptoms of depression	80.6%	86.2%	88.2%	87.2%

Symptoms of depression (mild – moderate – severe)	19.3%	13.8%	11.8%	12.8%

	T1	T2	T3	T4
Mean	2.05	2.13	1.95	2.04
SD	2.64	2.68	2.63	2.53

Table 3: Frequencies, mean and standard deviation (SD) of symptoms of anxiety per timepoint

	T1	T2	T3	T4
No symptoms of anxiety	92.9%	95.6%	96.8%	96.3%
Symptoms of anxiety	4.9%	4.4%	3.2%	3.7%

	T1	T2	T3	T4
Mean	0.15	0.14	0.11	0.12
SD	0,72	0.71	0.62	0.65

Table 4: Depression and anxiety total score (TS): mean (M), standard deviation (SD) and confidence intervals (CI) for fathers and mothers and p-values

	T1	T2	T3	T4
Depression TS	p < 0.001	p < 0.001	p < 0.001	p = 0.002
- Fathers M	2.22	1.79	1.64	1.68
(SD; CI)	(2.94; 2.03-2.40)	(2.33; 1.62-1.95)	(2.22; 1.48-1.81)	(2.22; 1.41-1.94)
- Mothers M	2.95	2.42	2.21	2.34
(SD; CI)	(3.11; 2.75-3.15)	(2.90; 2.23-2.60)	(2.90; 2.01-2.40)	(2.72; 2.05-2.64)
Anxiety TS	p < 0.001	p < 0.001	p < 0.001	p = 0.002
- Fathers M	0.08	0.06	0.04	0.02
(SD; CI)	(0.51; 0.04-0.11)	(0.50; 0.02-0.10)	(0.14; 0.01-0.06)	(0.20; -0.01-0.04)
- Mothers M	0.22	0.21	0.16	0.20

(SD; CI)	(0.86; 0.16-0.27)	(0.84; 0.16-0.26)	(0.75; 0.11-0.21)	(0.85; 0.10-0.29)

Table 5: Depression and anxiety total score (TS): mean (M), standard deviation (SD) and confidence intervals (CI) for having and not having a first-degree relative (FDR) and p-values

	T1	T2	T3	T4
Depression TS	p < 0.001	p = 0.077	p = 0.387	p = 0.748
- No FDR M	2.44	2.00	1.88	2.14
(SD; CI)	(2.89; 2.25-2.63)	(2.58; 1.82-2.18)	(2.60; 1.69-2.07)	(2.68; 1.79-2.49)
- FDR M	2.80	2.25	2.01	1.98
(SD; CI)	(3.00; 2.60-3.01)	(2.75; 2.07-2.42)	(2.66; 1.83-2.19)	(2.43; 1.73-2.23)
Anxiety TS	p = 0.582	p = 0.663	p = 0.418	p = 0.755
- No FDR M	0.15	0.15	0.13	0.13
(SD; CI)	(0.70; 0.10-0.19)	(0.71; 0.10-0.20)	(0.71; 0.08-0.18)	(0.72; 0.04-0.23)
- FDR M	0.16	0.14	0.08	0.11
(SD; CI)	`(0.74; 0.11-0.21)	(0.71; 0.09-0.18)	(0.52; 0.05-0.12)	(0.60; 0.05-0.17)

Table 6: Depression and anxiety total score (TS): p-values (Kruskal-Wallis Test) and means per country

	T1	T2	T3	T4
Depression TS	p = 0.006	p < 0.001	p < 0.001	p < 0.001
- Germany	2.48	1.70	1.55	1.61
- Sweden	2.50	2.21	2.39	1.98
- Belgium	2.83	2.38	2.25	3.50
- Poland	3.05	3.05	2.64	2.95
- UK	/	2.61	2.28	2.80
Anxiety TS	p = 0.002	p < 0.001	p < 0.001	p = 0.008
- Germany	0.11	0.04	0.02	0.06
- Sweden	0.29	0.24	0.22	0.16
- Belgium	0.20	0.25	0.19	0.25
- Poland	0.15	0.24	0.23	0.23
- UK	/	0.43	0.13	0.17

Figures:

Figure 1: Flowchart study design

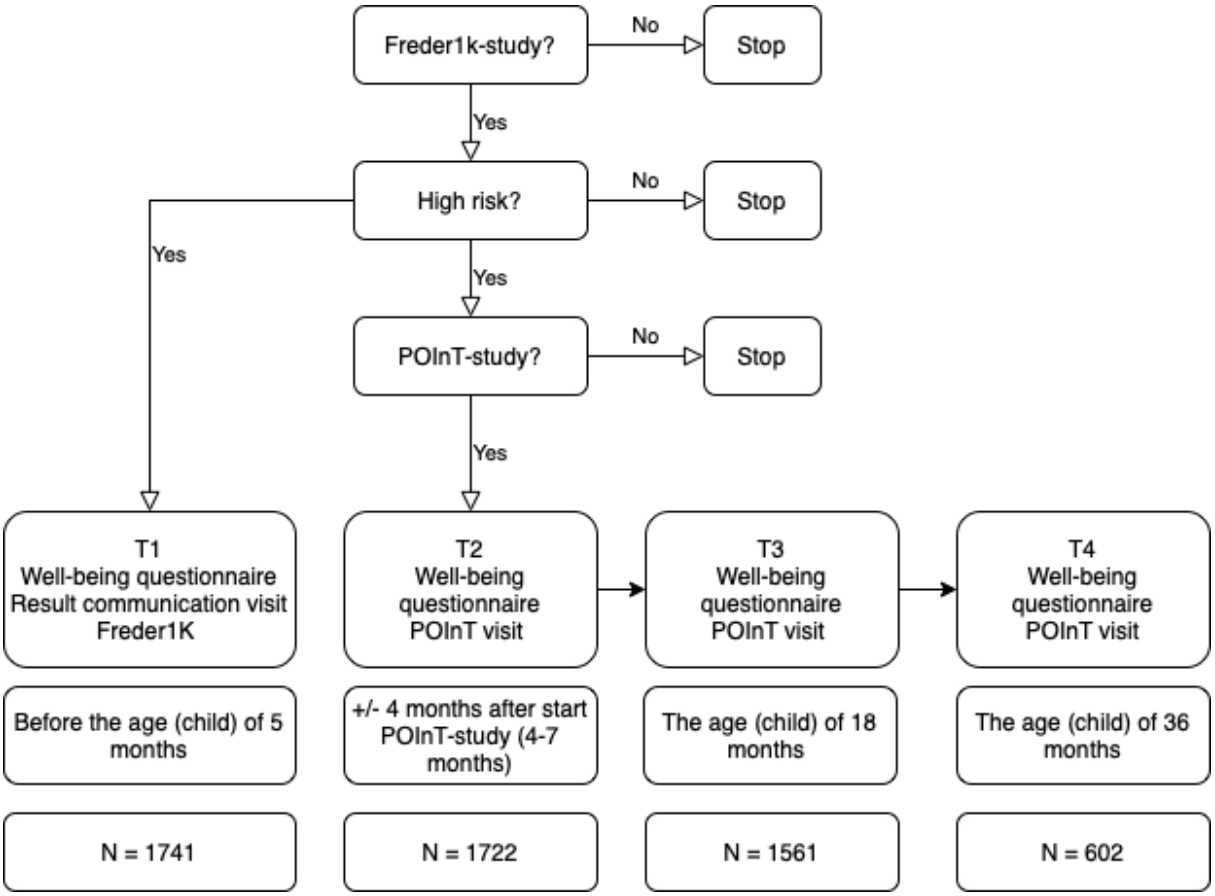


Figure 2: Violin plot depression total score (DTS) per timepoint

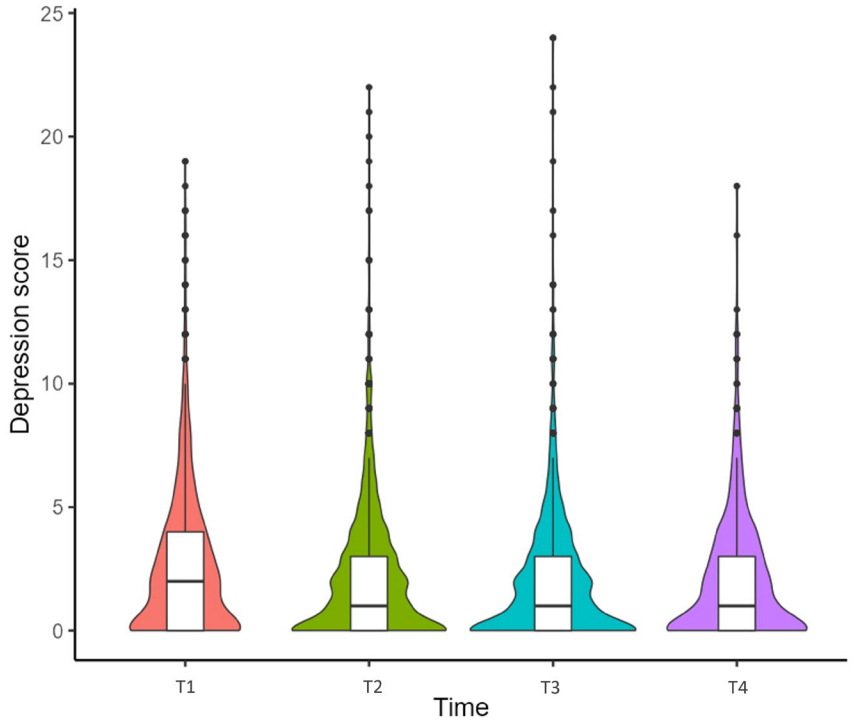


Figure 3: Violin plot anxiety total score (ATS) per timepoint

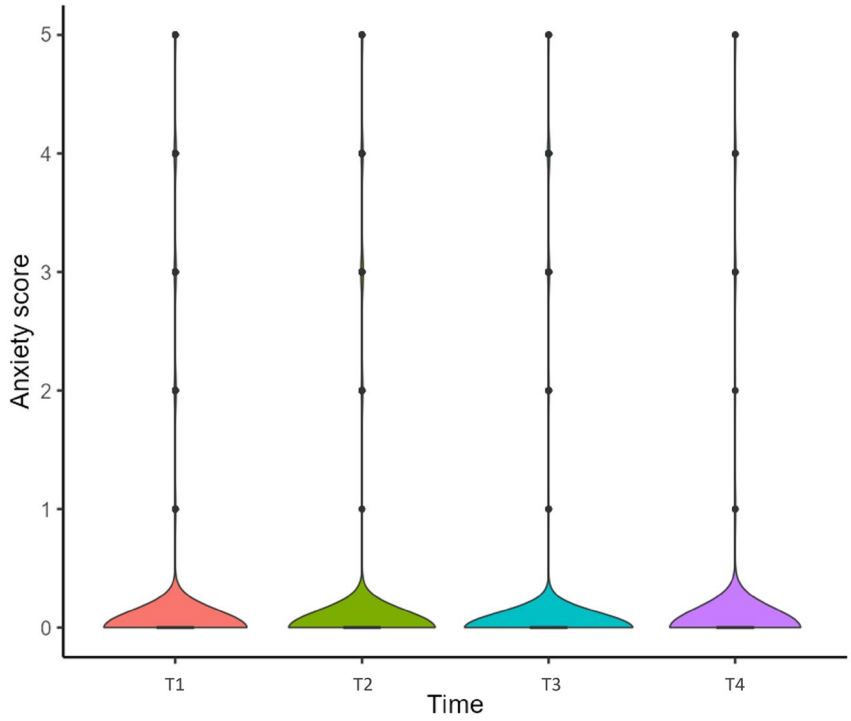
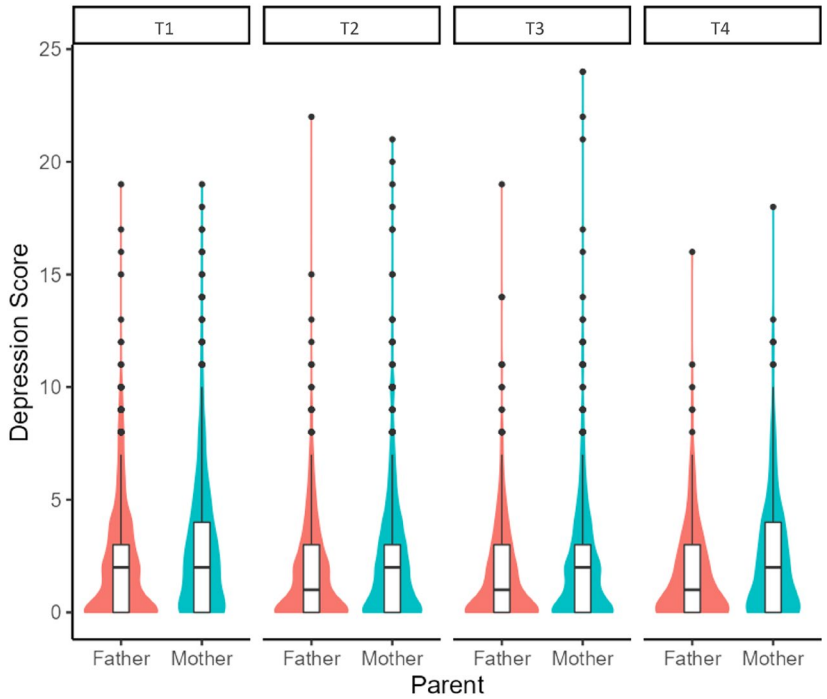


Figure 4 and 5: Violin plots depression and anxiety total score (DTS and ATS) per timepoint for fathers and mothers



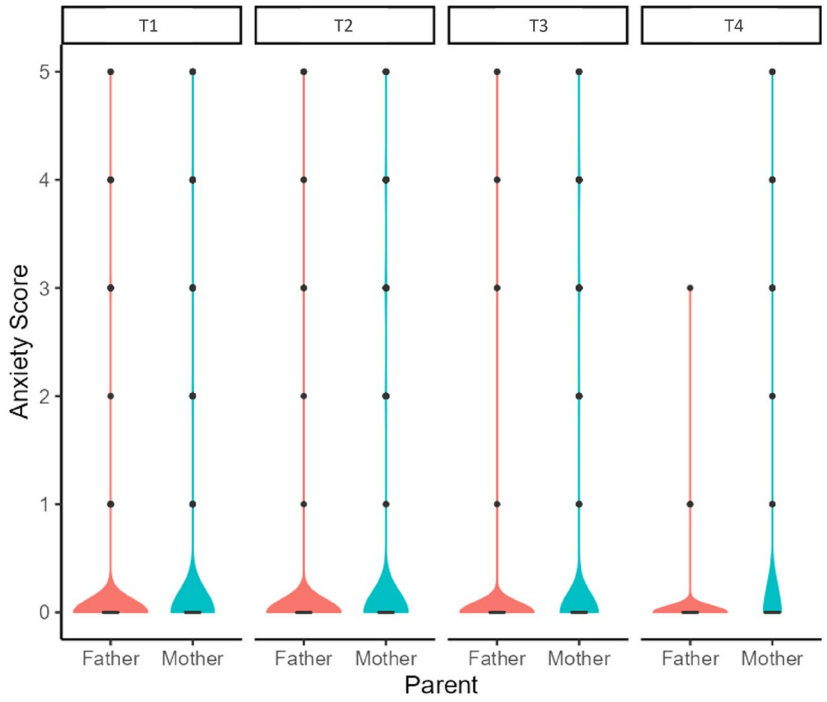


Figure 6 and 7: Mean depression and anxiety total score (DTS and ATS) per timepoint for fathers and mothers: evolution over time

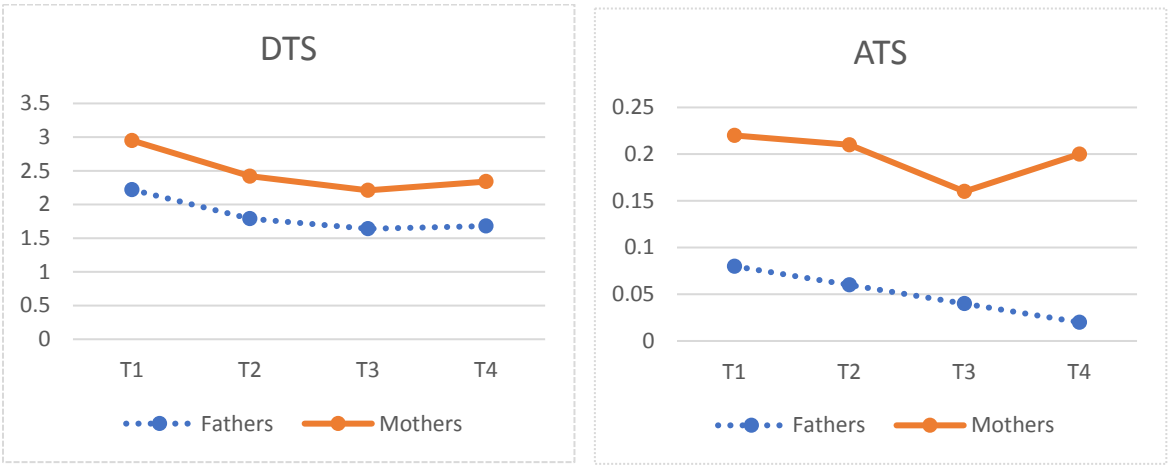
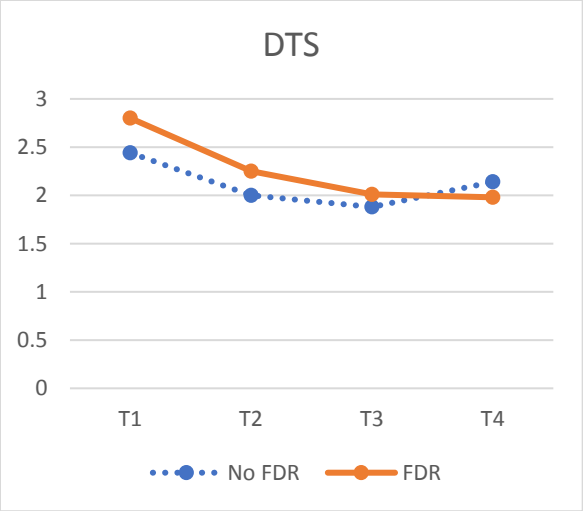
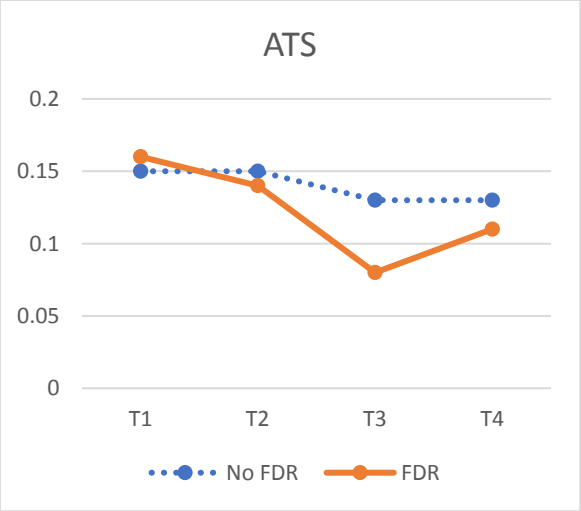


Figure 8 and 9: Mean depression and anxiety total score (DTS and ATS) per timepoint for having or not having a first-degree relative (FDR): evolution over time





Addendum

Addendum I:

- GPPAD-study Group

Addendum II:

- IIA: Well-being questionnaire result communication visit (GPPAD-02-study) (T1)
- IIB: Well-being questionnaire during the POInT-study (T2-5)

Addendum III:

- A structured assessment of the burden and need for support: psychological screening and care