Article published online: 2026-07-01

Thieme

Hormone and Metabolic Research

Original Article: Endocrine Care

Determinants of Infant Participation and Non-Participation in Primary Prevention Trials

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ABSTRACT

Understanding the determinants that influence parents' decisions to participate with their infants in primary prevention trials is essential for achieving representative study samples and ensuring the generalizability of outcomes. We analyzed quantitative and qualitative data collected from infants eligible for the Primary Oral Insulin Trial ($N = 2,750$) or the Supplementation with *B. INfantis* for Mitigation of Type 1 Diabetes Autoimmunity Trial ($N = 3,309$). Both trials were conducted within the Global Platform for the Prevention of Autoimmune Diabetes between 07/2017 and 04/2024. Among all eligible infants, a longer decision time (odds ratio: 1.01, 95 % confidence interval: 1.00–1.01, and $p = 0.002$), having a first-degree relative with type 1 diabetes (odds ratio: 2.18, 95 % confidence interval: 1.95–2.43, and $p < 0.001$), and a higher maternal age (odds ratio: 1.03, 95 % confidence interval: 1.01–1.05, and $p = 0.003$) were associated with a higher likelihood of participation, whereas infants born in fall (odds ratio: 0.85, 95 % confidence interval: 0.73–0.98, and $p = 0.03$) and families with longer travel distances to the study center (odds ratio: 0.97, 95 % confidence interval: 0.95-0.99, and $p = 0.01$) were less likely to participate. Participation was lower in the Supplementation with *B. INfantis* for Mitigation of Type 1 Diabetes Autoimmunity Trial than in the Primary Oral Insulin Trial (odds ratio: 0.86, 95 % confidence interval: 0.78–0.96, and $p = 0.005$), and stratified analyses indicated that some factors, such as recruitment during the COVID-19 pandemic, affected participation differently between studies. Analysis of qualitative data from 638 families identified additional factors, including the parental perception of the child's risk for type 1 diabetes and the burden of participation. In conclusion, this study identifies both general and study-specific determinants and reasons of participation and non-participation in infant primary prevention trials.

Keywords type 1 diabetes, clinical trial, children, islet autoantibodies

received April 08, 2026 | **accepted after revision** May 27, 2026 | **article published online** 2026

Bibliography Horm Metab Res **DOI** 10.1055/a-2884-2277 **Art ID** HMR-2026-04-0131

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Introduction

Randomized controlled trials represent the gold standard for generating evidence on the efficacy and safety of interventions, thereby guiding their implementation in clinical practice and public health programs.[1] However, relatively few trials are conducted in infants, as they are facing unique challenges, particularly with respect to recruiting a representative study sample within a short postnatal period.[2] Additional challenges include stringent ethical requirements and the need to carefully balance the protection of the child's health with the advancement of scientific knowledge.[3]

To support clinical research in infants, it is crucial to understand the factors influencing participation among eligible families. Previous studies have reported that non-participation is mainly due to modifiable factors, with parental refusal to participate being most common.[4] Parents must assess potential risks and make participation decisions during a vulnerable period shortly after birth. Reported barriers to the enrollment of infants in clinical trials include concerns about blood sampling[5, 6] and research in general.[7, 8] However, the reasons for declining participation in primary prevention trials, involving infants at an increased risk of disease but not yet affected, remain poorly understood.

Recent advances in genetic screening have made it possible to identify newborns at increased risk for type 1 diabetes (T1D), one of the most common chronic childhood diseases, with a rising global incidence.[9] This progress has enabled the initiation of primary prevention trials targeting at-risk infants.[10,11] While some data exist on enrollment experiences from observational studies involving children at increased risk for T1D,[12] no studies have examined factors influencing their participation in primary prevention trials.

To address this gap, this study examined factors influencing participation and non-participation in primary prevention trials that employ population-based recruitment, providing insights into families not affected by the disease, for whom awareness and motivation may be lower. Data from over 6,000 families with genetically at-risk infants eligible for enrollment in the multinational Primary Oral Insulin Trial (POInT) or the Supplementation with *B. INfantis* for Mitigation of the T1D Autoimmunity trial (SINT1A) were analyzed.

Methods

Study design

This study is a secondary analysis of data collected from families with infants identified to be eligible for inclusion in primary prevention studies by the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD).[11] GPPAD is a European network of collaborating clinical study centres, including Belgium (Leuven), Germany (Dresden, Hanover, and Munich), Poland (Warsaw), Sweden (Malmö) and the United Kingdom (Oxford and Newcastle). GPPAD offers genetic screening in collaboration with local maternity wards and primary care pediatricians to identify infants with a >10 % expected risk for developing multiple islet autoantibodies (IAs) by age 6 years as determined by the genetic risk score, family history and HLA genotype. Families with eligible children are invited to a consultation visit, during which qualified and trained GPPAD study personnel provide a detailed explanation of the clinical trial to the parents.

A concurrent mixed-method design was used, integrating quantitative analyses of determinants with qualitative content analysis of reasons for non-participation documented by the clinical study team.

Participants

All infants who underwent genetic screening between July 2017 and April 2024 using cord blood, capillary blood obtained during routine newborn screening, or blood collected during a well-baby visit at the pediatrician's office, and who met the eligibility criteria for either the randomized controlled POInT or SINT1A study, were included in this analysis (**Fig. 1**) .

The POInT study investigated whether the daily intake of oral insulin reduces the incidence of islet autoimmunity and/or T1D.[13] The SINT1A study evaluates whether the daily administration of *Bifidobacterium infantis* reduces the cumulative incidence of islet autoimmunity.[14] Eligibility for both trials was based on the genetic risk to develop multiple IAs >10 % by 6 years of age.[10,11] Additionally, infants had to be between 4.0 and 7.0 months of age at enrollment for POInT and between 7 days and 6 weeks of age for SINT1A. Detailed descriptions of the study protocols have been published previously.[13,14] Genetic screening for the POInT study took place between July 2017 and February 2021, and for the SINT1A study between March 2021 and April 2024.

Ethical approvals for genetic screening, the POInT and SINT1A studies were obtained from local ethical committees and regulatory authorities (**Supplementary Methods**, available in the online version only). The parents or legal representatives of each participant provided written informed consent.

Quantitative data

The variables included in the quantitative analysis were obtained through questionnaires administered at the time of genetic screening. Data available from all study centers included the child's sex, having a first-degree relative with T1D (yes/no) and study assignment (POInT or SINT1A). Information on the screening location (maternity ward or primary care pediatrician) was available for Munich, Hanover, Leuven and Oxford and information on maternal age at delivery for Munich, Hanover, Malmö, Leuven and Newcastle.

The travel distance to the study center (kilometer) was calculated with the R geosphere-package, using longitude and latitude developed in Excel (Geography). This information was available for Munich, Hanover, Malmö, Leuven, Newcastle and Oxford.

To account for the impact of the COVID-19 pandemic on study participation, the recruitment period was categorized into "Pre-COVID," "COVID" and "Post-COVID" according to the stringency index provided by the open-access Global Pandemic Policies Database.[15] "Pre-COVID" was defined by the date of birth before 03/18/2020, the start of the first lockdown in participating countries and the European Commission has implemented initial measures. "COVID" was defined by the date of birth between 03/18/2020 and 12/31/2022 and "Post-COVID" by the date of birth after 12/31/2022, the time when national government policies were back to pre-outbreak levels.

Time to decision was defined as the time interval (weeks) between the child's age at receipt of the screening result and the end of the eligibility period, which was defined by the child's age. In POInT, children were eligible for randomization between 4.0 and 7.0 months of age and in SINT1A between 7 days and 6 weeks of age.

Statistical analysis of quantitative data

Descriptive statistics were generated for all variables. Logistic regression models were used to identify factors associated with participation in the total cohort and separately for each study (POInT and SINT1A) to account for protocol-related differences. All statistical analyses were performed using R statistical software (version 4.3.1). An α-level of 0.05 was considered as statistically significant.

Qualitative data

For the qualitative analysis, open-text notes on reasons for declining participation, which were informally documented by the study personnel, were assessed. Notes were available for 638 out of 1,002 eligible families declining participation in POInT or SINT1A at the Munich study center.

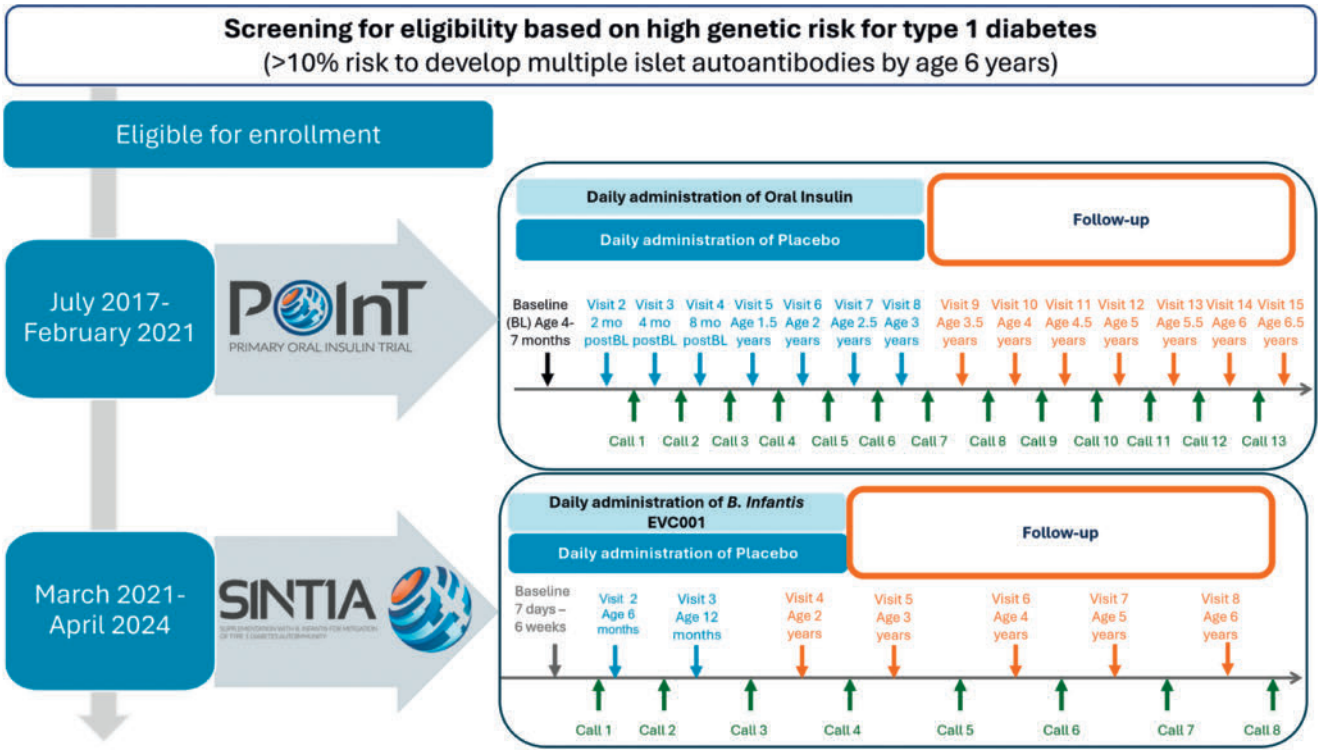

Fig. 1 A flow-chart of the GPPAD POInT and SINT1A trials.

A qualitative content analysis was conducted using a codebook developed through both inductive and deductive approaches.[16, 17] First, a literature review was performed to identify previously published categories of facilitators or barriers of study participation.[4, 7, 18–23] The collected notes were then reviewed to generate additional categories for items not captured by existing frameworks. Coding was carried out by the main coder (Wörl). Multiple categories could be assigned to each family. To assess inter-coder reliability, coding was performed by a second researcher (Hummel) on 40 notes (Cohen's Kappa [κ] = 0.86).

Results

Between July 2017 and April 2024, 6,059 infants were identified as eligible for participation in either the POInT or SINT1A trial. Of these, 2,199 (36.3 %) were enrolled (49.2 % women and 50.8 % men), including 1,050 of 2,750 (38.2 %) children who were eligible for POInT and 1,149 of 3,309 (34.7 %) for SINT1A (**Table 1**). Among all eligible infants, 1,996 (32.9 %) had a first-degree relative with T1D, while 4,063 (67.1 %) did not (**Table 1**). The number of eligible and enrolled children by the study site is shown in **Supplementary Fig. S1** (available in the online version only). The characteristics of all eligible children are shown in **Table 1**.

Factors associated with trial enrollment

Among all eligible children, a longer time for decision on participation (odds ratio [OR], 1.01; 95 % confidence interval [CI], 1.00–1.01; and $p = 0.002$), having a first-degree relative with T1D (OR, 2.18; 95 % CI, 1.95–2.43; and $p < 0.001$) and higher maternal age (OR, 1.03; 95 % CI, 1.01–1.05; and $p = 0.003$) were each associated with a greater likelihood of trial participation (**Table 1** and **Supplementary Fig. S2**, available in the online version only). Infants born in the fall (OR, 0.85; 95 % CI, 0.73–0.98; and $p = 0.03$), families with a longer travel distance to the study center (OR, 0.97; 95 % CI, 0.95–0.99; and $p = 0.01$) and infants who were screened for SINT1A were less likely to participate (OR, 0.86; 95 % CI, 0.78–0.96; and $p = 0.005$). No associations were observed between sex or screening location and participation.

The association between having a first-degree relative with T1D and study participation remained significant when analyzing POInT and SINT1A separately (OR, 2.86; 95 % CI, 2.43–3.36; and $p < 0.001$ for POInT, **Table 2**, **Supplementary Fig. S2**, available in the online version only, and OR, 1.67; 95 % CI, 1.43–1.95, and $p < 0.001$ for SINT1A, **Table 3**, **Supplementary Fig. S2**, available in the online version only). Stratified analyses revealed that other associations observed in the total cohort were either absent or only apparent in one trial. Higher maternal age was linked to greater participation only in POInT (OR, 1.04; 95 % CI, 1.01–1.07; and $p = 0.007$, **Table 2**), while a longer decision-time was associated with higher participation only in SINT1A (OR, 1.32; 95 % CI, 1.24–1.40; and $p < 0.001$; **Table 3**). Being born in winter and longer travel distance were associated with lower participation only in SINT1A (OR, 0.78; 95 % CI, 0.63–0.96; and $p = 0.02$ and OR, 0.96; 95 % CI, 0.94–0.99; and $p = 0.02$). Among the 1,125 children eligible for SINT1A with available information on the screening location, 68 children were screened by a primary care pediatrician. This was associated with a lower participation (OR, 0.47; 95 % CI, 0.24–0.85; and $p = 0.02$; **Table 3**).

Table 1 Characteristics of eligible infants for POInT or SINT1A stratified by enrollment status—the total cohort

	Eligible *n* = 6,059	Enrolled *n* = 2,199		Declined *n* = 3,860		Univariate analysis	
	n	*n*	%/Median [IQR]	*n*	%/Median [IQR]	OR [95 % CI]	*p* Value
Sex							
Female	2,999	1,083	49.2	1,916	49.6	1 (Reference)	
Male	3,029	1,116	50.8	1,913	49.6	1.03 [0.93–1.15]	0.55
First-degree relative with T1D[a]							
No	4,063	1,229	55.9	2,834	73.4	1 (Reference)	
Yes	1,996	970	44.1	1,026	26.6	2.18 [1.95–2.43]	<0.001
Mother T1D	890	403	18.3	487	12.6		
Father T1D	940	481	21.9	459	11.9		
Sibling T1D	218	119	5.4	99	2.6		
Maternal age (y)	2,341	1,027	32.1 [29.5–35.2]	1,314	31.9 [28.7–34.9]	1.03 [1.01–1.04]	0.003
Study assignment							
POInT	2,750	1,050	47.7	1,700	44.0	1 (Reference)	
SINT1A	3,309	1,149	52.3	2,160	56.0	0.86 [0.78–0.96]	0.005
Birth season							
Spring	1,587	613	27.9	974	25.2	1.04 [0.91–1.20]	0.54
Summer	1,721	647	29.4	1,074	27.8	1 (Reference)	
Fall	1,514	512	23.3	1,002	26.0	0.85 [0.73–0.98]	0.03
Winter	1,237	427	19.4	810	21.0	0.88 [0.75–1.02]	0.09
Screening location							
Maternity ward	2,153	755	87.5	1,398	87.8	1 (Reference)	
Pediatrician	303	108	12.5	195	12.2	1.03 [0.80–1.32]	0.84
Time to decision (wk)	5,667	2,047	5.7 [4.9–23.4]	3,620	5.4 [4.6–23.4]	1.01 [1.00–1.01]	0.002
Distance to study center (per 30 km)	2,782	1,167	54.8 [17.9–115.1]	1,615	73.0 [27.2–164.3]	0.97 [0.95–0.99]	0.01

Abbreviations: CI, confidence interval; IQR, interquartile range; POInT, Primary Oral Insulin Trial; SINT1A, Supplementation with *B. INfantis* for Mitigation of Type 1 Diabetes Autoimmunity Trial.

Note: Data are shown as percentages or median within enrolled and declined groups and as odds ratio (OR) for participation.

[a]T1D: type 1 diabetes.

Since the recruitment periods for POInT and SINT1A covered different phases of the COVID-19 pandemic, the pandemic period was included as a variable in the stratified analysis. Among infants eligible for POInT, those born before the pandemic were more likely to participate than those born during the pandemic (OR, 1.51; 95 % CI, 1.27–1.81; and $p < 0.001$; **Table 2**), while in SINT1A infants born after the pandemic were less likely to participate than those born during the pandemic (OR, 0.78; 95 % CI, 0.68–0.91; and $p = 0.001$; **Table 3**).

Parental reasons for non-participation

Several categories of reasons for non-participation were identified (**Table 4**). One category was related to the trial information and consent process, including limited time to make a decision and language barriers. Additionally, some parents perceived the risk of their child for the disease as too low to justify participation, emphasizing that their child was still healthy. Furthermore, several parents declined participation after consultation with their primary care pediatrician.

Another major category reflected the perceived burden of study participation for either the child or the parents. This included pre-existing conditions, such as young maternal age or the presence of a chronic illness within the family. Logistical barriers included long travel distances and time to the study center, the need to administer study medication, and the frequency of study visits.

Parents also expressed general concerns about research participation. These included discomfort with randomization—particularly concerns of receiving no benefit when assigned to the placebo group—as well as a general lack of trust or limited interest in research. Specific concerns were more common among families eligible for POInT, including possible harm or adverse effects to the child related to study participation and treatment, particularly regarding the administration of oral insulin to a "healthy" child (**Table 4** and

Table 2 Characteristics of eligible infants for POInT stratified by enrollment status

	Eligible *n* = 2,750	Enrolled *n* = 1,050		Declined *n* = 1,700		Univariate analysis	
	n	*n*	%/Median [IQR]	*n*	%/Median [IQR]	OR [95 % CI]	*p* Value
Sex							
Female	1,362	519	49.4	843	49.6	1 (Reference)	
Male	1,373	531	50.6	842	49.5	1.02 [0.88–1.20]	0.76
First-degree relative with T1D[a]							
No	1,716	495	47.1	1,221	71.8	1 (Reference)	
Yes	1,034	555	52.9	479	28.2	2.86 [2.43–3.36]	<0.001
Mother T1D	455	234	22.3	221	13.0		
Father T1D	481	266	25.3	215	12.7		
Sibling T1D	129	76	7.2	53	3.1		
Maternal age (y)	939	449	32.1 [29.4–35.4]	490	31.6 [28.4–35.0]	1.04 [1.01–1.07]	0.007
Birth season							
Spring	729	295	28.1	434	25.5	1.09 [0.89–1.33]	0.43
Summer	816	314	29.9	502	29.5	1 (Reference)	
Fall	659	230	21.9	429	25.2	0.86 [0.69–1.06]	0.16
Winter	546	211	20.1	335	19.7	1.01 [0.81–1.26]	0.95
Screening location							
Maternity ward	1,098	403	80.9	695	83.2	1 (Reference)	
Pediatrician	235	95	19.1	140	16.8	1.17 [0.88–1.56]	0.29
Covid-19 pandemic							
Pre-Covid-19	1,996	814	77.5	1,182	69.5	1.51 [1.27–1.81]	<0.001
Covid-19	754	236	22.5	518	30.5	1 (Reference)	
Time to decision (wk)	2,358	898	23.9 [20.1–25.1]	1,460	24.1 [21.6–25.3]	1.00 [0.99–1.01]	0.70
Distance to study center (per 30 km)	1,235	543	49.2 [14.4–106.1]	692	56.8 [8.0–137.8]	0.99 [0.95–1.02]	0.44

Abbreviations: CI, confidence interval; IQR, interquartile range; POInT, Primary Oral Insulin Trial.
Note: Data are shown as percentages or median within enrolled and declined groups and as odds ratio (OR) for participation.
[a]T1D: type 1 diabetes.

Supplementary Table S1, available in the online version only). Some parents also questioned the value of participation given the yet unproven efficacy of the intervention. Additionally, concerns about blood draws were mentioned.

Finally, a commonly documented reason for non-participation was the inability to establish contact with the families.

Discussion

This study found that 36.3 % of families with eligible infants participated in GPPAD primary prevention trials, a considerably higher rate than previously reported for clinical trials. For example, oncology trials often report participation below 10 % across age groups, including children.[24] Notably, two-thirds of eligible infants in this study did not have a first-degree relative with T1D, suggesting that many families may have had limited prior awareness of the disease. In addition, this study identified multiple factors associated with participation or non-participation of families in the trials. Some of these factors appear modifiable and could be addressed in the study design to enhance enrollment, such as providing sufficient time for decision-making, reducing logistical challenges, and minimising the perceived burden on families. In addition, general research concerns and trial-specific concerns were identified as barriers, underscoring the importance of clear communication throughout the information and consent process. This study also highlighted reasons for non-participation that are less amenable to change, as they primarily reflect personal attitudes or concerns.

Both the quantitative and qualitative data emphasized the role of logistical factors in parental decision-making. Adequate time to decide, travel distance/time to the study center, and the complexity of study procedures were identified as key determinants of participation. This is consistent with previous reports identifying logis-

Table 3 Characteristics of eligible infants for SINT1A stratified by enrollment status

	Eligible *n* = 3,309	Enrolled *n* = 1,149		Declined *n* = 2,160		Univariate Analysis	
	n	*n*	%/Median [IQR]	*n*	%/Median [IQR]	OR [95 % CI]	*p* value
Sex							
Female	1,637	564	49.1	1,073	49.7	1 (Reference)	
Male	1,656	585	50.9	1,071	49.6	1.04 [0.90–1.20]	0.60
First-degree relative with T1D[a]							
No	2,347	734	63.9	1,613	74.7	1 (Reference)	
Yes	962	415	36.1	547	25.3	1.67 [1.43–1.95]	<0.001
Mother T1D	435	169	14.7	266	12.3		
Father T1D	459	215	18.7	244	11.3		
Sibling T1D	89	43	3.7	46	2.1		
Maternal Age (years)	1,402	578	32.1 [29.6–35.0]	824	32.0 [28.9–34.8]	1.02 [0.996–1.04]	0.11
Birth season							
Spring	858	318	27.7	540	25.0	1.01 [0.83–1.23]	0.91
Summer	905	333	29.0	572	26.5	1 (Reference)	
Fall	855	282	24.5	573	26.5	0.85 [0.69–1.03]	0.09
Winter	691	216	18.8	475	22.0	0.78 [0.63–0.96]	0.02
Screening location							
Maternity ward	1,055	352	96.4	703	92.8	1 (Reference)	
Pediatrician	68	13	3.6	55	7.2	0.47 [0.24–0.85]	0.02
Covid-19 pandemic							
Pre-Covid-19	0	0	0.00	0	0.00	–	
Covid-19	1,903	705	61.4	1,198	55.5	1 (Reference)	
Post-Covid-19	1,406	444	38.6	962	44.5	0.78 [0.68–0.91]	0.001
Time to decision (weeks)	3,309	1,149	5.0 [4.4–5.3]	2,160	4.9 [4.0–5.3]	1.32 [1.24–1.40]	<0.001
Distance to study center (per 30 km)	1,547	624	56.8 [23.0–121.9]	923	85.3 [45.9–169.3]	0.96 [0.94–0.99]	0.02

Abbreviations: CI, confidence interval; IQR, interquartile range; SINT1A, supplementation with *B. infantis* for Mitigation of Type 1 Diabetes Autoimmunity Trial.

Note: Data are shown as percentages or median within enrolled and declined groups and as odds ratio (OR) for participation.

[a] T1D: type 1 diabetes.

tical challenges and time commitment as common barriers to participation in clinical trials.[6,8,25–27] The lower participation among families with children born in autumn or winter may reflect a higher perceived burden of attending study visits during colder months. To address these concerns, strategies such as reducing the number of blood draws,[5,6,12] coordinating visits with local primary care pediatricians, or offering home visits, may help to improve participation rates.

Parents of infants eligible for POInT were more likely to participate than those eligible for SINT1A, which may reflect differences in enrollment strategies across trials and sites. Evidence from a systematic review suggests that proactive and continuous engagement by study teams can enhance enrollment rates.[23] Our findings also suggest that some of the identified determinants are trial-specific, likely reflecting variations in study design, including differences in the type of intervention, inclusion time periods, and visit frequency. In POInT, some parents perceived their child's risk as too low to justify participation and expressed concerns about potential risks associated with an unproven therapy or the burden of repeated blood draws. In contrast, these concerns were less frequently reported in SINT1A, suggesting that the probiotic intervention was perceived as less invasive than oral insulin. This aligns with previous findings indicating that parents of healthy children are more likely to emphasize safety aspects and are more concerned about the potential risks of the treatment,[6,25,26,28–30] whereas parents of children already diagnosed with a disease tend to focus on the potential benefits of an intervention.[31]

Table 4 Reasons for declining study participation—results from the qualitative data analysis

Category	Subcategory	Definition	Examples
Trial information and consent process related	Not enough time to make decision about participation [23]	Insufficient time to decide about participation before the final enrollment deadline	"Declined participation due to limited decision time"—SINT1A Protocol
	Language barriers [20, 23]	Parents had insufficient German language skills and comprehension difficulties	"Father recalled, both parents hardly speak German."—SINT1A Protocol "Mother recently moved from Africa to Germany, speaks no German [...]"—SINT1A Protocol
	Parental perception of the child's risk [19, 22–23]	Perceived risk of 10 % considered too low to justify participation or study burden; OR focus placed on the 'healthy child'	"10 % risk is too low for the burden of the study"—POInT Protocol
	Consultation with Primary Care Pediatrician [a]	Declined participation following pediatrician's advice or due to satisfaction with existing care	"Declined participation because not recommended by pediatrician"—POInT Protocol "Declined participation, feels in good hands with the pediatrician and considers that sufficient"—POInT Protocol
Burden of study participation [8, 23]	for the child	Specific burden on the child associated with study participation OR pre-existing conditions that prevent participation	"Mother doesn't want to burden her child at such an early age"—SINT1A Protocol
	for the mother/parents	Specific burdens on the mother/parents associated with study participation OR pre-existing family or personal circumstances that prevent participation	"Reached mother; she is very young and passed the receiver to the grandmother [..] MM/DD/YYYY Declined participation due to burden"—POInT Protocol "Declined participation [...]; participation in the SINT1A study considered too much burden for the family"– SINT1A Protocol
Logistics of study participation [23]	Travel time/Distance to study center	Challenges related to travel time or distance to the study center	"Declined, the distance is too far for them"– SINT1A Protocol "Phone call with mother; declined due to driving distance"– POInT Protocol
	Study logistics [8, 21, 23]	Increased logistical effort associated with frequent study visits, long follow-up phases, required documentation, or regular medication administration OR general concerns about the effort involved	"Interested in participating in SINT1A, but not feasible for the family in terms of time and scheduling "– SINT1A Protocol "Declined; mother could not guarantee daily administration of medication"—POInT Protocol
General research concerns/ Lack of interest in research	Discomfort with randomization/ placebo [8, 23]	Discomfort withrandomization OR concerns that the child will not benefit from the treatment when receiving placebo	"Risk too high for placebo"– POInT Protocol "Called mother; afraid of receiving placebo"—POInT Protocol
	Lack of trust in research [22, 23]	Parental lack of trust in medical research in general	"Father is skeptical about clinical trials and doesn't want to take part"– POInt Protocol "Immediately after being informed of the eligibility, the mother expressed skepticism about participating in trials [...]"—POInT Protocol
	Guinea pig concerns [8, 23]	Parental fear that the child might be treated as a "guinea pig", reflecting concerns about potential exploitation, insufficient protection, privacy violation or lack of genuine consent	"Parents don't want the child to be a guinea pig"—SINT1A Protocol "Findings communicated; mother, a geriatric nurse, doesn't want the child to be a guinea pig and wishes to consult the pediatrician first"—POInT Protocol

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Table 4 Continued

Category	Subcategory	Definition	Examples
	No response / No interest [a]	Indicated no interest in trial participation, declined without providing a reason, or did not respond by the agreed deadline	"Declined participation by email without providing a reason"– SINT1Ab Protocol; "Mother reached; not interested in participation, stated she will get in touch if needed"—POInT c Protocol
Concerns about study participation	Perceived Risk to the child [8,23]	Parental fear of possible harm or adverse consequences to the child from study participation	"Declined; parents do not want to give medication to a healthy child"—POInT Protocol "Declined; does not feel comfortable with the administration of insulin [...]"– POInT Protocol
	Lack of direct benefit for the child [23]	Parents perceive limited or no direct benefit of participation for the child OR unclear benefit for the child due to the use of an unproven treatment	"Declined due to unproven therapy"—POInT Protocol "Declined; not sure whether the treatment has any beneficial effect at all"—POInT Protocol
	Concerns about blood draws [18]	Parental concerns regarding regular blood draws OR expectations of pain or stress for the child associated with blood draws	"Declined [...] by mail. Parents are too afraid of the blood samples"– POInT Protocol
No contact established[a]	Before consultation	The consultation visit did not occur due to the families being unreachable or no longer in contact	"MM/DD/YYYY genotyping results were communicated, MM/DD/YYYY and MM/DD messages were left on the answering machine, MM/DD answering machine, MM/DD answering machine, MM/DD answering machine"– POInT Protocol
	After consultation	A consultation visit was planned and completed, but the families could not be reached afterward	"MM/DD consultation visit completed; Family considering participation; to be contacted after vacation. Messages left on answering machine on MM/DD, MM/DD, MM/DD, and MM/DD"– POInT Protocol "Consultation visit conducted with the mother only; she e planned to call back after discussing with the father [...] did not contact us again"– SINT1A Protocol
Unknown[a]		No information available; missing data/documentation	

[a] Inductive development of the categories.

[b] SINT1A = Supplementation with B. INfantis for Mitigation of Type 1 Diabetes Autoimmunity [c] POInT = Primary Oral Insulin Trial

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Decision-time appeared to be a stronger determinant of participation in SINT1A, where infants could only be enrolled up to 6 weeks of age, compared with POInT, which allowed enrollment up to 7 months of age. This is consistent with previous evidence highlighting the importance of adequate time for parental decision-making.[32] It may also explain why participation in SINT1A was lower when screening occurred through primary care pediatricians than through maternity wards. Because families typically do not visit their primary care pediatrician until several weeks after birth, there is a shorter window for deciding about participation.

Another trial-specific finding was the impact of the COVID-19 pandemic on participation. In POInT, infants born before the pandemic were more likely to participate, whereas in SINT1A infants born after the pandemic were less likely to participate than those born during it. One possible explanation is that families remained burdened in the period following the pandemic,[33] making them less willing to commit to trial participation with a newborn.

Having a first-degree relative with T1D emerged as a strong predictor of trial participation and aligns with previous reports from clinical trials in adults aiming to prevent Alzheimer's disease[34] and rheumatoid arthritis,[35] and with participation-rates reported by the observational TEDDY study, following children at increased risk for T1D.[12] Parental familiarity with the condition has also been shown to influence their decisions in a pediatric trial to prevent diabetic ketoacidosis (DKA), where children with prior episodes of DKA were enrolled at significantly higher rates than those without DKA.[36] These findings further suggest that increasing disease awareness may enhance the enrollment of infants from the general population. One potential strategy to achieve this is through partnerships with patient advocacy organizations.[37]

Enrollment was also positively associated with increasing maternal age. This association was more pronounced among children eligible for POInT and is consistent with findings from the TEDDY study.[12] Higher maternal age has been linked to increased health literacy and higher maternal educational attainment.[38,39] Since low health literacy is associated with poorer understanding of health information, literacy-informed counselling of families with eligible children could support enrollment decisions by addressing common barriers, such as a lack of interest in clinical research, mistrust and parental perception of their child's risk for the disease.[20,29]

Finally, the differences in enrollment rates between sites may reflect variations in their recruitment strategies. Findings from a previous study suggest that sites with higher enrollment and adherence were more likely to collaborate with healthcare providers and to employ a broader range of recruitment strategies, such as speaking at patient advocacy events and conferences, as well as providing information through educational materials and websites.[37]

This study benefits from its mixed-methods design, which allowed for a more comprehensive understanding of enrollment dynamics. Several quantitative findings were supported by qualitative data, strengthening the validity of the results. Combining data from two trials enabled analysis of a large sample size and the comparison of trial-specific factors. Furthermore, the inclusion of data from all GPPAD countries provides a transnational perspective and generalizability across different European settings.

However, several limitations should be considered when interpreting the findings. As a secondary data analysis, the study could not account for other factors that may be important in this context, such as mother's psychological well-being in the early postpartum period or the family's socioeconomic status. Although some associations were modest, they highlight modifiable factors that could be targeted to improve enrollment in clinical trials. Additionally, notes taken on reasons for non-participation were not standardized, resulting in variability in length and detail across families. Nevertheless, the large number of available notes likely mitigated this limitation. The generalizability of some results is limited due to missing data for some variables in a few study sites. Moreover, because the qualitative analysis was based solely on data from the Munich site, findings may be less transferable due to potential country-specific differences in reasons for non-participation.

Conclusions

This study provides insights for improving the enrollment of infants in primary prevention trials. The identified factors for participation and non-participation underscore the need to carefully evaluate study protocols, particularly the necessity and frequency of procedures, to ensure scientific robustness while minimizing the burden on families. Additionally, raising awareness of the disease and providing tailored, health literacy appropriate information about the condition and the trial may help families make informed decisions and improve enrollment.

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Statements and Additional Information

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

Acknowledgement We thank the families for their participation in type 1 diabetes research and helping to develop therapies for prevention. Acknowledgements of GPPAD POInT and SINT1A Study Groups are provided in the supplemental text.

Funding Information The Leona M. and Harry B. Helmsley Charitable Trust | #2018PG-T1D022 and #2003-04286 | Helmholtz Munich, German Research Center for Environmental Health, Germany | Bundesministerium für Bildung und Forschung | FKZ: 01KX1818 | EASD-Novo Nordisk Foundation Diabetes Prize for Excellence to AGZ (Helmholtz Munich) | NNF22SA0081044 | The Leona M. and Harry B. Helmsley Charitable Trust | #2018PG-T1D023 and #2007-04031 | German Center for Diabetes Research (DZD e.V.) to Helmholtz Munich

Clinical Trail Registration Registration number (trial ID): POInT: NCT03364868; SINT1A: NCT04769037, Trial registry: ClinicalTrials.gov (http://www.clinicaltrials.gov/), Type of Study: Prospective, Randomized, Multi-Center Study

Supplementary Material is available at https://doi.org/10.1055/a-2884-2277

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