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Abstract

Aims:
The onset of clinical type 1 diabetes (T1D) is preceded by the occurrence of disease-specific autoantibodies. The level of autoantibody titers is known to be associated with progression time from the first emergence of autoantibodies to the onset of clinical symptoms, but detailed analyses of this complex relationship are lacking. We aimed to fill this gap by applying advanced statistical models.
Methods:
We investigated data of 613 children from the prospective TEDDY study who were persistent positive for IAA, GADA and/or IA2A autoantibodies. We used a novel approach of Bayesian joint modeling of longitudinal and survival data to assess the potentially time- and covariate-dependent association between the longitudinal autoantibody titers and progression time to T1D.
Results:
For all autoantibodies we observed a positive association between the titers and the T1D progression risk. This association was estimated as time-constant for IA2A, but decreased over time for IAA and GADA. For example the hazard ratio [95% credibility interval] for IAA (per transformed unit) was 3.38 [2.66, 4.38] at 6 months after seroconversion, and 2.02 [1.55, 2.68] at 36 months after seroconversion.
Conclusions:
These findings indicate that T1D progression risk stratification based on autoantibody titers should focus on time points early after seroconversion. Joint modeling techniques allow for new insights into these associations.

Keywords (separated by '-') Autoantibodies - Joint modeling - Type 1 diabetes

Footnote Information

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ORIGINAL ARTICLE

Joint modeling of longitudinal autoantibody patterns and progression to type 1 diabetes: results from the TEDDY study

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Abstract

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Results For all autoantibodies we observed a positive association between the titers and the T1D progression risk. This association was estimated as time-constant for IA2A, but decreased over time for IAA and GADA. For example the hazard ratio [95% credibility interval] for IAA (per transformed unit) was 3.38 [2.66, 4.38] at 6 months after seroconversion, and 2.02 [1.55, 2.68] at 36 months after seroconversion.

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Conclusions These findings indicate that T1D progression risk stratification based on autoantibody titers should focus on time points early after seroconversion. Joint modeling techniques allow for new insights into these associations.

Keywords Autoantibodies · Joint modeling · Type 1 diabetes

Introduction

Type 1 diabetes (T1D) is one of the most common chronic diseases in childhood, with worldwide increasing incidence [1]. The disease is preceded by a preclinical period of islet autoimmunity, which most commonly develops in early infancy [2, 3]. The presence of islet autoantibodies is associated with the progression to clinical diabetes [4]. However, the time from the first emergence of autoantibodies, called seroconversion, to the onset of clinical symptoms varies considerably between individuals, ranging from weeks to decades [4].

It is also known that the combination of different autoantibodies as well as the autoantibody titer is associated with progression time [5]. For insulin autoantibodies (IAA), both their titers around seroconversion and their mean levels over time have been found to be associated with progression to T1D [2, 6], and similar findings have been recently reported for other islet autoantibodies [7–9]. Nevertheless, detailed analyses of autoantibody titers over time are lacking.

Here, we investigated data of more than 600 islet-autoantibody-positive children followed up within the prospective The Environmental Determinants of Diabetes in the Young (TEDDY) study [10, 11]. In contrast to previous analyses, we used joint models of longitudinal and survival data. This class of models has the advantage to avoid potential bias due to characteristics of the longitudinal markers (here autoantibodies), such as random biological fluctuations, informative censoring and discrete measurement time points [12]. By applying a novel approach of joint modeling, we gained further insights into the potentially complex relationship between longitudinal islet-autoantibody measures and the time to T1D progression, particularly with respect to time-varying associations of both.

Methods

TEDDY is an ongoing prospective cohort study funded by the National Institutes of Health with the primary goal to identify environmental causes of T1D. The TEDDY study enrolled 8676 children with increased genetic risk for T1D who were recruited in six clinical research centers located in the USA, Finland, Germany and Sweden between 2004 and 2010 shortly after birth. Detailed information on study design, eligibility and methods has been previously published [11, 13, 14]. Written informed consents were obtained for all participants from a parent or primary caretaker, separately, for genetic screening and for participation in prospective follow-up. The study was approved by local Institutional Review Boards and is monitored by the External Advisory Board formed by the National Institutes of Health. For this analysis, we used the data of all children who had developed one or more persistent islet autoantibodies by the time of our data access (December 31, 2014). At that time point the median age of the children analyzed at their last visit was 6.5 years with a range from 0.75 to 10.2 years.

Definition of islet autoimmunity

Development of persistent islet autoimmunity was assessed every 3 months and defined by the presence of at least one islet autoantibody among autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA) and insulinoma-associated protein 2 (IA2A) on two or more consecutive visits confirmed by two laboratories. Date of persistent autoimmunity to an autoantibody was defined as the draw date of the first sample of the two consecutive samples which deemed the child persistent confirmed positive for this autoantibody. As described in more detail elsewhere [7], the respective autoantibody titers were standardized to be comparable across study laboratories (University of Bristol, UK; and University of Colorado, Denver, USA) by subtracting the laboratory- and antibody-specific threshold and dividing by the laboratory- and autoantibody-specific standard deviation and were log-transformed afterward.

Study outcome

The main outcome of this analysis was the time to development of T1D after seroconversion in months. T1D diagnosis was based on American Diabetes Association criteria [15].

Statistical analyses

Of the 8676 children enrolled, 613 had developed one or more autoantibodies at the time of our data access. We created three subsets of the data where we restricted the data to children who had seroconverted to IAA ($n = 442$), GADA ($n = 466$) or IA2A ($n = 288$), respectively. These subsets were not mutually exclusive, as children had potentially seroconverted to multiple autoantibodies. Children were assigned to each subset irrespectively of whether the

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specific autoantibody was among the first islet autoantibodies to appear or appeared at a later time during follow-up. For example, if a child developed autoantibodies to IAA first and autoantibodies to GADA later, the child would be assigned to both the IAA and GADA subset.

We used a novel shared parameter joint model approach to assess the association between the longitudinal autoantibody titers from seroconversion with the time to T1D. Joint models allow the incorporation of longitudinal titers as time-varying covariates into the survival model of progression to T1D by estimating a longitudinal model and a proportional hazards model, using a joint likelihood for both submodels [16]. We further extended this model to a more flexible joint model, where we were able to assess heterogeneous and nonlinear individual biomarker trajectories and to explore complex associations between the biomarkers and the time to event [17]. We refer to Appendix for further details. Using this novel approach we specified the autoantibody titers over time as smooth, nonlinear, subject-specific trajectories in the longitudinal model. Furthermore we allowed the association between the modeled trajectories and the time to T1D to be time-varying in our main analysis. In additional explorative analyses we allowed the association to differ between subjects with different characteristics, and to differ over time between subjects with different characteristics.

We fitted these models for each of the three autoantibodies IAA, GADA and IA2A, separately, within each autoantibody-specific subset. In the longitudinal submodels, we assessed the associations of each autoantibody titer with (a) age at seroconversion of the respective autoantibody, (b) a binary variable indicating whether the autoantibody was among the first autoantibodies to appear, and (c) two time-varying binary variables indicating which of the other two autoantibodies were present at each observed time point. In each proportional hazards submodel, we assessed the associations of the smooth subject-specific autoantibody trajectories from the longitudinal model with progression time from seroconversion of the respective autoantibody to T1D. Baseline covariates were (a) the age at seroconversion of the respective autoantibody and (b) whether the autoantibody was among the first autoantibodies to appear. We further assessed whether the association between the autoantibody trajectories and the time to T1D differed over time between subjects with and without a first-degree relative with T1D or between girls and boys. Additionally we checked for differences in the association between HLA genotypes. Due to the limited size of certain HLA subgroups we modeled this association as time-constant.

All models were estimated within a Bayesian framework using the R-package *bamlss* [18]. Weakly informative normal priors were used for all coefficients. We report the posterior mean estimates/hazard ratios and 95% credibility intervals (CI) for all modeled parameters. Bayesian CIs can be interpreted as the interval in which the population parameter lies with a given probability (here 95%). We assessed convergence of the Markov chains by visual inspection of traceplots and conducted sensitivity analyses with regard to prior specification. All calculations were carried out with R version 3.2.5 [19].

Results

Table 1 shows the study characteristics in each subset, i.e., the subsets of children who developed IAA, GADA or IA2A autoantibodies, respectively, at any time during follow-up. In most cases, either IAA, GADA or both were present at the time of the first seroconversion, whereas IA2A occurred at a later time point. The children seroconverted to the different autoantibodies at different median ages ($p < 0.001$, Kruskal–Wallis Test) with IAA seroconversion taking place at a lower median age. Apart from that, children with different autoantibodies were similar regarding the progression time to T1D and other variables.

The individual autoantibody patterns over time after seroconversion were heterogeneous, but on average IAA titers declined after an initial increase, and GADA and IA2A titers increased shortly after seroconversion and remained relatively stable thereafter (Supplementary Fig. 1).

In the joint modeling of autoantibody titers over time and the time to T1D, we observed for all autoantibodies a positive association between the titer and the risk of progression to T1D. Titers over time were lower for subjects who seroconverted at an older age for the respective autoantibody, and higher if the respective autoantibody appeared at the initial seroconversion, and if other autoantibodies were present (Table 2). For each autoantibody, a higher age at the respective seroconversion was also associated with lower risk of progression to clinical T1D. For example, children had a hazard ratio [95% CI] of 0.84 [0.72, 0.98] if they seroconverted one year later for IAA.

We further investigated whether the association between the estimated trajectories of autoantibodies and the progression to T1D was time-varying or constant. By using our approach, we observed that the association was time-varying for IAA and GADA with the association being highest early after seroconversion and decreasing over time (Fig. 1) and stronger for IAA than GADA: The hazard ratio for IAA (per transformed unit) was 3.38 [2.66; 4.38] at 6 months after seroconversion, 3.02 [2.44, 3.81] at 12 months after seroconversion and 2.02 [1.55, 2.68] at 36 months after seroconversion (Table 3) with an average decrease in the hazard ratio of 10% [95% CI 2, 18%] every 6 months. The hazard ratio for GADA (per transformed unit) was 1.63

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Table 1 Description of the study population by type of persistent autoantibody

Variable	Total	Type of persistent autoantibody		
		IAA	GADA	IA2A
Total number of children	613	442	466	288
Age at respective seroconversion (years)	2.2 (1.2, 3.8)	2.0 (1.1, 3.5)	2.7 (1.6, 4.2)	2.8 (1.9, 4.5)
Girls	268 (44%)	200 (45%)	212 (45%)	112 (39%)
Country				
US	206 (34%)	136 (31%)	166 (36%)	94 (33%)
Finland	153 (25%)	125 (28%)	109 (23%)	85 (30%)
Germany	47 (8%)	40 (9%)	32 (7%)	22 (8%)
Sweden	207 (34%)	141 (32%)	159 (34%)	87 (30%)
Child having a first-degree relative with T1D	128 (21%)	105 (24%)	97 (21%)	71 (25%)
HLA-DR genotype				
DR3/4	311 (51%)	241 (55%)	251 (54%)	148 (51%)
DR4/4	106 (17%)	74 (17%)	81 (17%)	64 (22%)
DR4/8	92 (15%)	71 (16%)	51 (11%)	46 (16%)
DR3/3	76 (12%)	30 (7%)	64 (14%)	16 (6%)
Other	28 (5%)	26 (6%)	19 (4%)	14 (5%)
Additionally autoantibody positive for				
IAA			302 (65%)	252 (88%)
GADA		302 (68%)		237 (83%)
IA2A		252 (57%)	237 (51%)	
Autoantibody present at first seroconversion		353 (80%)	344 (74%)	40 (14%)
Number of children who developed T1D	175 (29%)	162 (37%)	134 (29%)	127 (44%)

Values are reported as *n* (% of non-missing observations) for categorical variables and median (interquartile range) for continuous variables

Table 2 Posterior mean estimates of coefficients (β) and hazard ratios with corresponding 95% credibility intervals from joint models of autoantibody trajectories (IAA, GADA and IA2A, as estimated in longitudinal submodels) and progression to T1D (survival submodels)

Autoantibodies	Covariate	Longitudinal models		Survival models	
		β	95% CI	HR	95% CI
IAA	IAA present at first seroconversion	**0.35**	0.20, 0.51	0.66	0.42, 1.02
	IAA seroconversion age (years)	**−0.10**	−0.13, −0.07	**0.84**	0.72, 0.98
	GADA positive (time-varying variable)	**0.31**	0.24, 0.37	[a]	[a]
	IA2A positive (time-varying variable)	**0.17**	0.12, 0.22	[a]	[a]
GADA	GADA present at first seroconversion	**0.34**	0.19, 0.47	0.72	0.51, 1.03
	GADA seroconversion age (years)	**−0.06**	−0.09, −0.03	**0.61**	0.52, 0.72
	IAA positive (time-varying variable)	**0.25**	0.20, 0.32	[a]	[a]
	IA2A positive (time-varying variable)	**0.06**	0.02, 0.11	[a]	[a]
IA2A	IA2A present at first seroconversion	**0.31**	0.11, 0.50	1.07	0.61, 1.80
	IA2A seroconversion age (years)	**−0.05**	−0.08, −0.01	**0.66**	0.56, 0.78
	IAA positive (time-varying variable)	**0.22**	0.09, 0.36	[a]	[a]
	GADA positive (time-varying variable)	**0.29**	0.18, 0.41	[a]	[a]

Bold font indicates that the 95% CI does not include 0 (for β) or 1 (for HR)

CI credibility interval, *HR* hazard ratio

[a] Covariate only included in the longitudinal submodel

[1.20, 2.30] at 6 months after seroconversion, 1.40 [1.07, 1.85] at 12 months after seroconversion and 0.85 [0.61, 1.17] at 36 months after seroconversion with an average decrease of 9% [1, 15%] every 6 months. For IA2A, the positive association between autoantibody titer and T1D progression was estimated as time-constant: The hazard ratios for IA2A (per transformed unit) were 1.56 [1.04, 2.42] at 6 months after seroconversion, 1.53 [1.10, 2.16] at 12 months after seroconversion, and 1.44 [1.005, 2.16] at 36 months after seroconversion with a negligible average

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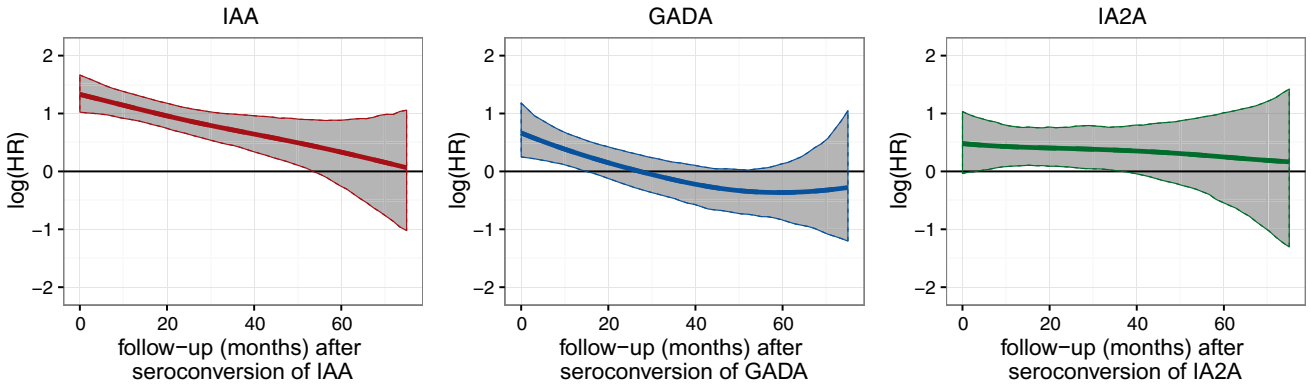

Fig. 1 Posterior mean estimates (*lines*) and 95% credibility intervals (*shaded areas*) of $\eta_a(t)$, the time-varying log hazard ratio (HR) of the association between longitudinal autoantibody trajectories and type 1 diabetes

Table 3 Posterior mean hazard ratios (HR) with corresponding 95% credibility intervals (CI) at different time points after seroconversion of each autoantibody for the association between autoantibody trajectories from the longitudinal model and progression time to type 1 diabetes

Autoantibodies	Time point (months)	HR	95% CI
IAA	0	**3.78**	2.78, 5.28
	6	**3.38**	2.66, 4.38
	12	**3.02**	2.44, 3.81
	24	**2.43**	1.94, 3.02
	36	**2.02**	1.55, 2.68
	48	**1.69**	1.17, 2.50
	60	1.39	0.77, 2.42
GADA	0	**1.94**	1.28, 3.25
	6	**1.63**	1.20, 2.30
	12	**1.40**	1.07, 1.85
	24	1.07	0.80, 1.41
	36	0.85	0.61, 1.17
	48	0.73	0.50, 1.04
	60	0.69	0.43, 1.14
IA2A	0	1.62	0.96, 2.81
	6	**1.56**	1.04, 2.42
	12	**1.53**	1.10, 2.16
	24	**1.49**	1.08, 2.13
	36	**1.44**	1.005, 2.16
	48	1.37	0.82, 2.33
	60	1.28	0.58, 2.74

Bold font indicates that the 95% CI of the respective association does not include the 1

decrease of 2% [−8, 13%] every 6 months. As indicated by the credibility intervals in Fig. 1, positive associations with T1D progression were observed for IAA up to 54 months after seroconversion, for GADA up to 18 months after seroconversion and for IA2A between 6 and 36 months after seroconversion. The traceplots indicated satisfactory convergence of the Markov chains (Supplementary Figs. 4–6), and sensitivity analyses showed robustness against different prior specifications (Supplementary Fig. 7).

We further observed differences in the time-varying association of autoantibodies with progression to T1D between children with and without a first-degree relative with T1D. For all autoantibodies the associations were higher among children with a first-degree relative at early time points and decreased more strongly within this group (Fig. 2, upper panel). For IAA, the associations between the two groups differed from seroconversion until about 15 months thereafter, as indicated by the credibility bands of the differences (Fig. 2, lower panel), but only from 3 to 7 months after seroconversion for GADA and from 3 to 13 months after seroconversion for IA2A. For all autoantibodies HLA subgroups were similar in the association between autoantibody trajectories and the time to T1D (Fig. 3). An exception was a higher association for subjects with IAA autoantibodies and the DR3/3 genotype, a genotype which is less prevalent among IAA positive children (n = 30, 7%). In accordance with the difference in the hazard, the mean titer levels between progressors and non-progressors differed more strongly within the small subgroup of DR3/3 than within other HLA genotypes with non-progressors showing an especially low level (Supplementary Fig. 2). We did not observe consistent differences in the association over time between girls and boys (Supplementary Fig. 3).

Discussion

In the present study the complex relationship between longitudinally measured autoantibodies and the risk of progression to T1D diabetes was explored using a novel joint modeling approach. We observed potentially time-varying

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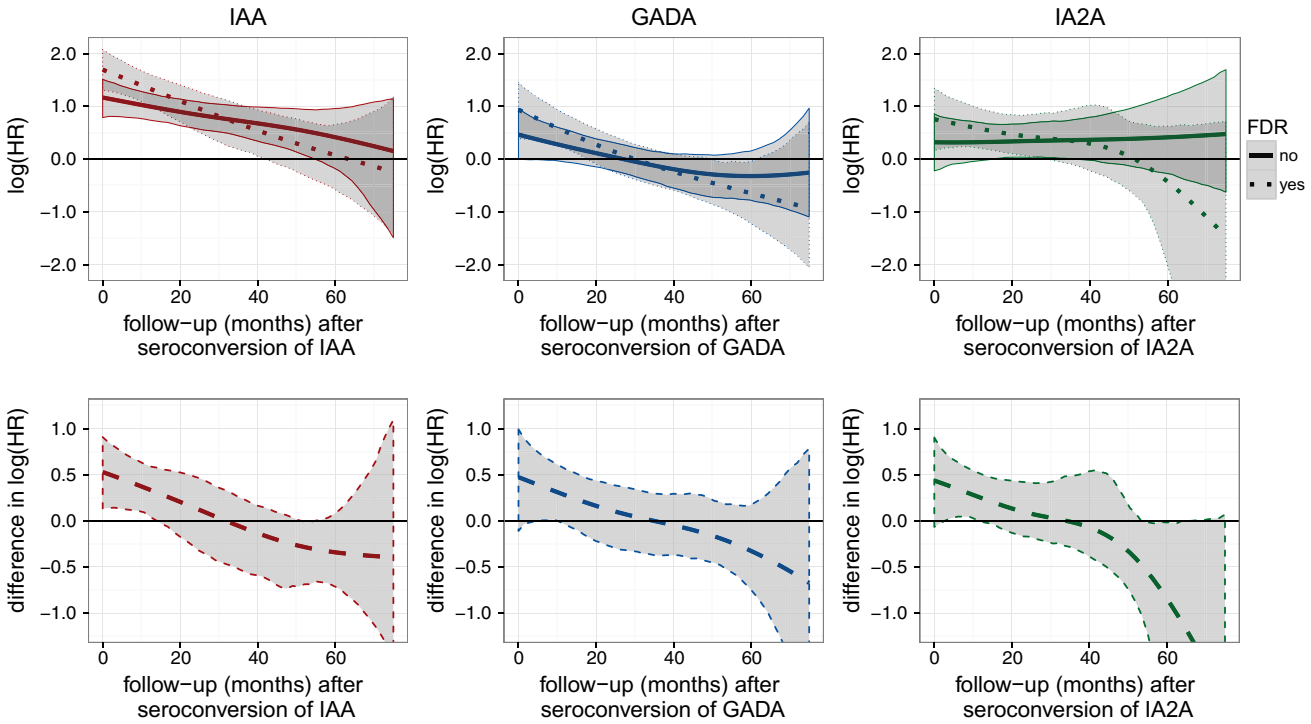

Fig. 2 Posterior mean estimates (*lines/dots*) and 95% credibility intervals (*shaded areas*) of η_α (t, FDR), the time-varying log hazard ratio (HR) of the association between longitudinal autoantibody trajectories and type 1 diabetes (T1D) progression stratified for children that had a first-degree relative (FDR) with T1D or not (*upper panel*) and of the difference of the association between the groups over time, η_α (t, FDR = 1) − η_α (t, FDR = 0) (*lower panel*)

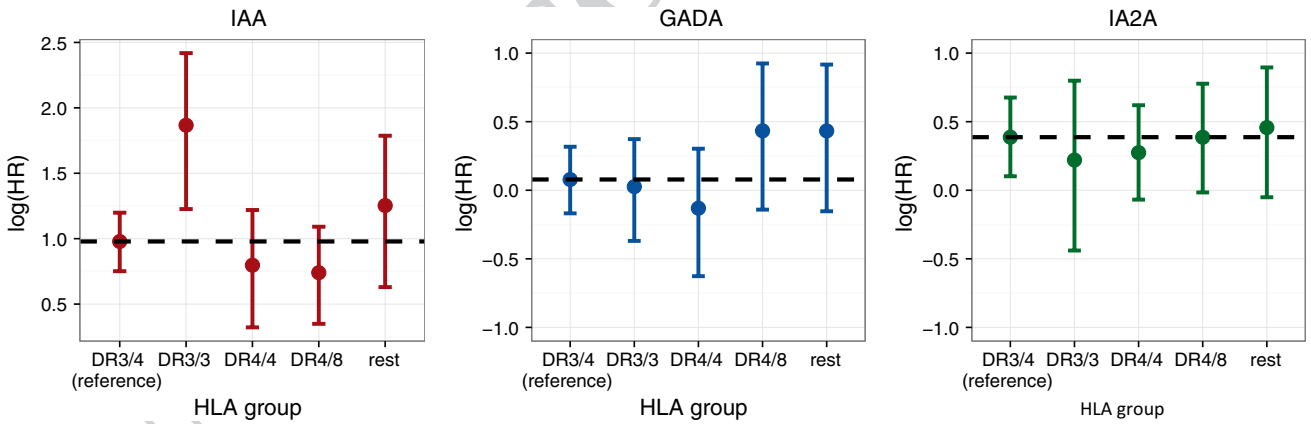

Fig. 3 Posterior mean estimates and 95% credibility intervals of η_α (HLA), the time-constant log hazard ratio (HR) of the association between longitudinal autoantibody trajectories and type 1 diabetes progression, per HLA genotype. The *dashed line* represents the estimated log hazard ratio of the reference group

positive associations between the autoantibody titers of IAA and GADA, and the risk of T1D progression, indicating that the T1D progression risk associated with autoantibody titers was highest shortly after seroconversion of the respective autoantibody. The hazard ratio was highest for IAA, especially at early time points. Additionally, we observed that the associations of the autoantibody titer and the T1D risk early after seroconversion were more pronounced in children with first-degree relatives with T1D.

These results were in line with earlier results from other cohorts, where initial and mean IAA and IA2A titers were shown to be associated with the risk of progression [2, 6, 20] as well as from a more recent and methodologically advanced study based on the TEDDY data. In this study

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the relationship between titers of the same autoantibodies over time and the risk of progression to T1D was modeled assuming a time-constant association [7]. By using mean levels of the respective autoantibodies as time-varying predictors in a Cox model, the authors could show a positive association between autoantibody titers and the time to T1D progression for IAA and IA2A in their analyses.

Potential limitations of this previous approach are, however, that (a) only subject's mean titers until a certain time point are taken into account and not all observed values over time, (b) in a time-varying Cox model the time-varying predictor is assumed constant between observations, and (c) the association between autoantibodies and the risk of progression is assumed to be time-constant. These limitations were addressed by our joint modeling approach. Here, we flexibly modeled the trajectories of all three autoantibodies in each subject as a smooth function of time, i.e., obtaining predictions for the autoantibody titers between the measurements at discrete time points, and could use all this information as a time-varying covariate in the survival model. Additionally, we allowed their association with the risk of T1D progression to vary over time and between groups of subjects (children with and without first-degree relatives with T1D as well as boys and girls). In consequence, we were able to explore the association between autoantibodies and the risk of T1D beyond the previous results. For example, we observed that increased GADA titers may predict T1D progression within the first 1.5 years after seroconversion, but not thereafter. As this association averages to 0 over the whole time range this association was potentially not captured in the simpler modeling from the previous analysis. Furthermore, our modeling approach revealed that the time-varying associations appear to be more pronounced in children with first-degree relatives with T1D compared to children without.

The modeling of autoantibodies as longitudinal biomarkers and the time to clinical T1D poses a challenge due to the nature of the data beyond the aspects mentioned above. Longitudinal biomarkers usually contain potential random variation both due to the laboratory measurement process as well as short- and long-term biological fluctuations and are only observed until an event occurs. Whereas not accounting for the random fluctuations in a time-varying Cox model might result in an underestimation of the hazard ratio [12], ignoring the latter might distort the estimation of covariate effects in the longitudinal model. By jointly analyzing the longitudinal and survival model we could address these issues and gained further insights as to how covariates affected both the autoantibody titers over time, and the risk of T1D progression. We found that earlier seroconversion for the respective autoantibody, if the respective seroconversion was the initial one, as well as the presence of other autoantibodies was associated with higher autoantibody titers. The age at the respective seroconversion was also inversely related to the risk of T1D progression for every autoantibody. While joint modeling approaches allow for detailed and unbiased estimations, they demand a high number of subjects, especially when complex associations are modeled in the survival part. TEDDY is the largest prospective study on the determinants of T1D worldwide and thus offers a unique opportunity to explore the application of joint modeling techniques on these complex relationships due to the high number of subjects and the detailed measurement schedule.

Currently, the presented flexible joint model only allows the assessment of one longitudinal biomarker at a time. In consequence, one limitation is that we were not able to combine all three markers into one joint model. We partly addressed this issue by including information on the presence of other autoantibodies and the order of their occurrence in our model. While they provide insights into the mechanisms of disease progression, a drawback of our results is that they cannot easily be translated from a cohort setting with frequent measurements into clinical practice, as the age at the respective seroconversion plays a crucial role in the prediction of T1D progression risk, but is not readily available in practice.

In conclusion, by using state of the art joint modeling techniques we were able to give insights into the complex relationship between longitudinal autoantibody titers and the risk of progression to clinical T1D. Risk stratification basing on autoantibody titers should focus on time points early after seroconversion.

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Author contributions AGZ and EB designed this manuscript proposal. MK analyzed the data and wrote the first and final draft of the manuscript together with AB, SG and AGZ. EB and KV contributed to the interpretation of the results and to subsequent drafts of the manuscript. NU contributed to specific programming aspects. MR, WAH, JXS, AL, JT, BA, AGZ and JPK are principal investigators of the TEDDY study, contributed to conception and design of the TEDDY study, data acquisition and funding for TEDDY, reviewed the manuscript and contributed to subsequent drafts. This work is part of MK's PhD thesis within the graduate school HELENA at the Helmholtz Zentrum München in collaboration with the Ludwig-Maximilians-Universität München, Germany.

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Compliance with ethical standards

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

Human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008 (5).

Informed consent Informed consent was obtained from all patients for being included in the study.

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