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ARTICLE

Maternal type 1 diabetes reduces the risk of islet autoantibodies: relationships with birthweight and maternal HbA_{1c}

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Abstract
Aims/hypothesis The risk of type 1 diabetes is reduced in the children of mothers with type 1 diabetes compared with children of fathers with type 1 diabetes. We asked whether children of mothers with type 1 diabetes also have a decreased risk of developing islet autoantibodies, and which factors associated with maternal diabetes contribute to a reduced islet autoantibody risk in offspring.
Methods Singleton offspring of a mother (n=1,008) or father with type 1 diabetes (n=578) from the BABYDIAB study were included. Children were followed from birth for the development of islet autoantibodies defined as two or more autoantibodies to insulin, glutamic acid decarboxylase or insulinoma antigen 2 in two or more blood samples.
Results Islet autoantibody risk was lower in children of mothers with type 1 diabetes (5 year risk, 3.2% vs 5.7% in children of fathers with type 1 diabetes; p=0.04). Among factors that differed between pregnancies from mothers with and without type 1 diabetes, birthweight was associated with islet autoantibody risk. Risk was reduced in children with birthweights in the lower (adjusted HR 0.33; 95% CI 0.14–0.75; p=0.009) and upper (HR 0.45; 95% CI 0.21–0.97; p=0.04) tertiles compared with the middle tertile. A sub-analysis of maternal HbA_{1c} suggested that moderately elevated third trimester maternal HbA_{1c} was also associated with a reduced islet autoantibody risk in children of mothers with type 1 diabetes (5.7–7%; HR 0.38; 95% CI 0.15–0.96; p=0.04 vs children of mothers with HbA_{1c}<5.7%).
Conclusions/interpretation The risk of islet autoimmunity is modified by maternally influenced events such as birthweight.

Keywords Birthweight · Glycaemic control · Islet autoantibodies · Type 1 diabetes

Abbreviations

GADA	glutamic acid decarboxylase autoantibodies
IAA	insulin autoantibodies
IA2A	insulinoma antigen 2 autoantibodies
VNTR	variable number of tandem repeats

Introduction

The pathogenesis of type 1 diabetes includes a preclinical phase, in which individuals develop autoimmunity to islet beta cell antigens, followed by variable progression to clinical disease [1]. The risk of type 1 diabetes is conferred by inherited susceptibility genes [2, 3]. However, risk is not Mendelian, and is therefore modified by non-Mendelian factors that include the environment [4]. A model that is potentially useful for investigating factors that affect islet autoimmunity and type 1 diabetes risk is presented in children of parents who have type 1 diabetes. Risk is up to twofold greater in children of fathers with type 1 diabetes

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than in children of mothers with type 1 diabetes [5–7]. This intriguing fact suggests that either differences in inheritability of paternal vs maternal susceptibility genes or maternal imprinting or maternal diabetes (i.e. the environment) modify a child's inherited genetic risk of developing type 1 diabetes. Although there are reported differences in the transmission of *IDDM1* susceptibility genes [8] and evidence for maternal imprinting of the *IDDM2* susceptibility gene [9], their combined effect does not appear to explain the magnitude of the observed differences in risk; it is likely that the maternal diabetes environment contributes to type 1 diabetes protection.

Environmental exposure both in utero and in the early perinatal period is very different in children of mothers with type 1 diabetes compared with children of non-diabetic mothers. Diabetic pregnancies are characterised by increased and fluctuating glycaemia, placental transfer of insulin, altered lipid metabolism and a range of other metabolic aberrations [10–13]. Despite improvements in recent decades, diabetic pregnancies are still complicated by considerably higher rates of severe perinatal complications [14–17] and are associated with increased rates of stillbirth and perinatal mortality, increased prevalence of congenital malformation, an increased rate of Caesarean section, increased numbers of preterm deliveries, and increased birthweights.

An opportunity to examine the impact of maternal diabetes and associated factors on the development of islet autoimmunity is provided by the German BABYDIAB study [18–20]. Since 1989, the German BABYDIAB study has prospectively followed from birth, children of mothers and/or fathers with type 1 diabetes for the development of islet autoantibodies and diabetes.

Here, we have asked whether children of mothers with type 1 diabetes have a decreased risk of developing islet autoantibodies, and subsequently analysed which factors associated with maternal type 1 diabetes could account for a reduced islet autoantibody risk in offspring. The findings suggest that the very early metabolic events caused by a maternal diabetes environment could have a role in the development of immune tolerance to pancreatic antigens.

Methods

The BABYDIAB study examines the natural history of islet autoimmunity, from birth, in children of parents with type 1 diabetes [18–20]. Families were eligible to participate if one or both parents had type 1 diabetes. Recruitment into the study began in 1989 and ended in 2000. Recruitment was facilitated through advertisements in paediatric and patient journals, and in paediatric and neonatal clinics and participation was on a voluntary basis. Cord blood was obtained in obstetric departments from eligible families that consented to participation. Venous blood samples from the child during follow-up were obtained at paediatric clinics at age 9 months and 2, 5, 8, 11, 14 and 17 years. Questionnaires were completed at birth and at each paediatric visit. The study was coordinated by the Diabetes Research Institute in Munich through direct contact with the families and the family paediatrician. Offspring were considered as participants of the BABYDIAB study if they were recruited at birth and participated in at least the 9 month follow-up. A total of 1,650 offspring fulfilled these criteria including 1,586 offspring who were from singleton births and who had only one parent with type 1 diabetes. Only these 1,586 births were included in the current analysis. These included 1,008 newborn of 865 mothers with type 1 diabetes and 578 newborn of 488 healthy mothers and a father with type 1 diabetes (Table 1). At the time of analysis, 1,431 children had participated in the follow-up visit at year 2; 1,247 at year 5; 808 at year 8; and 276 at year 11. The cumulative dropout rate was 16.0% by age 5 years and 20.9% by age 8 years. Islet autoantibodies were measured in samples taken at all completed scheduled visits, and yearly after developing islet autoantibodies. The median follow-up time from birth to last sample was 6.8 years (range: 0.75–16.6 years) and from birth to last contact was 8.6 years (range: 0.75–18.5 years). All families gave written informed consent to participate in the BABYDIAB study. The study was approved by the ethical committee of Bavaria, Germany (Bayerische Landesärztekammer Nr. 95357).

Autoantibody measurements Autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA) and insulinoma antigen 2 (IA2A) were measured by radiobinding assays, as previously described [19, 21]. The upper limits of normal corresponded to the 99th percentile of control children, and were 1.5 local units/ml for IAA, 8.5 local units/ml or 25 WHO units/ml for GADA, and 2.5 local units/ml or 4 WHO units/ml for IA2A. Using these thresholds for positivity, the assays had sensitivities and specificities of 70% and 99% (IAA), 86% and 93% (GADA), 72% and 100% (IA2A), and 84% and 100% for multiple islet autoantibodies in the Third Diabetes Autoantibodies Standardization Program Proficiency Workshop [22]. The inter-assay CV for samples with low autoantibody titre was 11% for IAA, 18% for GADA and 16% for IA2A. All measurements were performed on coded samples that were operator blinded.

Main outcome measure The development of islet autoantibodies was considered the outcome marker for this study. Children were considered islet autoantibody positive if at least two consecutive samples after birth were found

Table 1 Pregnancy-related exposure and demographic data in the study cohort: comparisons between type 1 diabetic and non-diabetic (paternal type 1 diabetes) pregnancies

Variable	Maternal type 1 diabetes		Paternal type 1 diabetes		*p* value
	n		*n*		
Gestational age at delivery, weeks (median and IQR)	904	39 (38–40)	556	40 (39–41)	<0.0001
Preterm delivery (%)	904	13.3	556	4.9	0.0001
Birthweight, g (median and IQR)	915	3,500 (3,130–3,920)	562	3,410 (3,137–3,752)	0.001
Caesarean section (%)	861	47.7	507	19.3	<0.0001
Apgar score, 5 min<10 (%)	522	53	373	27.3	<0.0001
Apgar score, 10 min<10 (%)	521	30	372	8.3	0.0001
Maternal age at delivery, years (median and IQR)	1,006	29.6 (26.9–32.3)	561	30.4 (27.7–32.9)	0.002
Any breastfeeding (%)	933	76.6	524	87	<0.0001
Full breastfeeding>3 months (%)	904	42.5	509	58.7	<0.0001
Mother smoked while pregnant (%)	1,005	12.6	577	10.1	0.08
Child weight gain at 9 months, g (median and IQR)	873	5,920 (5,170–6,715)	525	6,000 (5,230–6,695)	0.3
Sex (female/male)	1,008	492/516	578	281/297	0.8
First-born child (%)	711	66.5	450	65.6	0.7
DR4 positive (%)	880	51.4	520	49.6	0.5
Insulin VNTR (%)	762		424		0.3
AA		64		62	
AB		32.7		33	
BB		3.3		4.7	
Maternal HbA_{1c} at delivery, % (median and IQR)	567	5.8 (5.2–6.2)		Not determined	

IQR Interquartile range

positive for one or more islet autoantibodies (IAA, GADA or IA2A) and if at least one sample was found positive for two or more islet autoantibodies. Children who were positive in only one sample or who only had one of the islet antibodies were classified as islet autoantibody negative.

HLA and INS variable number of tandem repeats (VNTR) genotyping HLA DR and DQ genotypes were determined in 1,400 children of parents with type 1 diabetes. The remaining 186 children did not provide a suitable sample for HLA typing. *HLA-DRB1*, *HLA-DQA1* and *HLA-DQB1* alleles were typed using PCR-amplified DNA and non-radioactive sequence-specific oligonucleotide probes as described previously [23, 24]. *INS* VNTR typing was performed in 1,186 children. The remaining 400 children did not provide enough DNA for *INS* VNTR typing. *INS* VNTR typing was determined by HphI digestion of PCR amplification products of the region of interest, as described previously [23]. The single nucleotide polymorphism identified by this method is in almost complete linkage disequilibrium with the *INS* VNTR [25].

Collection of demographic data and environmental exposure data during pregnancy and the early perinatal period Perinatal and anthropometric data were collected from each child's paediatric record at birth, at age 9 months, 2 years and every 3 years thereafter. Records were completed by trained staff at delivery and by paediatricians at clinical visits after birth. Data with respect to maternal age of delivery, gestational age, Caesarean section, Apgar score at 5 and 10 min, sex of the child, and birthweight were recorded at birth. Gestational age was determined on the basis of the last menstrual period and expressed as weeks. Weight gain during the first 9 months was obtained at a paediatric visit at the age of 9 months of the child.

The age of onset of maternal type 1 diabetes, parity status, smoking behaviour during pregnancy, and for mothers with type 1 diabetes also third trimester HbA_{1c}, were self-reported in a questionnaire given to the mothers before or at delivery. HbA_{1c} was determined as part of clinical care of the patients and not as part of the BABYDIAB study. HbA_{1c} values were retrieved from laboratory reports held by patients. HbA_{1c} was measured locally by undisclosed methods from 1989 to 2000. Some mothers provided HbA_1 values only and these were not included in the analysis. HbA_{1c} values were provided for 567 of 1,008 births from mothers with type 1 diabetes.

Data on breastfeeding (yes, no) and the duration of full breastfeeding (weeks) and any breastfeeding were obtained by questionnaire at birth and at the age of 9 months and 2 years. Breastfeeding was defined according to WHO criteria [26] as 'full breastfeeding' if the infant received breast milk with or without supplements of water or water-based drinks, vitamins and medicines, but without formula, or other milk or solids, and as 'any breastfeeding' if the

infant received breast milk, irrespective of any other types of food including full breastfeeding.

Statistical analysis Time-to-event methods were used to calculate risks (life table analysis) and to compare islet autoantibody outcome for participants with different covariate categories (life table analysis and Cox proportional hazards model). Covariate categories were either dichotomous (yes/no) or based on tertiles calculated from the whole cohort. An exception was maternal HbA_{1c} where the distribution had outliers. Categories for HbA_{1c} were therefore set for outliers (>7%) and at the median of the remainder (<5.7% and 5.7–7%). In children with a positive outcome, the age at the first sample positive for one or more islet autoantibodies was used as the event time. Analysis considered censoring in losses to follow-up and in participants with antibody-negative status at the follow-up visit age of their last autoantibody-negative sample. The log-rank test was used for comparisons of covariate categories in life table analysis. HRs were calculated using a Cox proportional hazards model and where indicated were adjusted for maternal diabetes. The proportional hazards assumption in the Cox model was tested by examining the log minus log plot of each covariate for parallel curves, and by using a time-dependent Cox regression that included the covariate in question and the interaction between time and the covariate. The interaction was not significant for all covariates, indicating that the hazards were proportional.

Islet autoantibody incidence was determined by calculating the incremental increase in risk at the 9 month, 2 year, 5 year and 8 year visits corrected for the time interval between visits, and expressed as cases per 100/year. Comparisons between the islet autoantibody incidence at age 9 months of children of fathers with type 1 diabetes and children of mothers with type 1 diabetes was performed using Fisher's exact test. The Mann–Whitney *U* test was used to compare live singleton births from fathers with type 1 diabetes and mothers with type 1 diabetes for gestational age, birthweight, Apgar scores, maternal age at delivery, and child weight gain at age 9 months. The χ^2 test was used to compare live singleton births from fathers with type 1 diabetes and mothers with type 1 diabetes for the proportion of preterm births (gestational age ≤37 weeks), breastfeeding, maternal smoking during pregnancy, sex of the child, the proportion of children who were first-born, and DR4 status. The χ^2 test for trend was used to compare *INS* VNTR genotype between children of fathers with type 1 diabetes and children of mothers with type 1 diabetes. Pearson correlation was used to correlate maternal HbA_{1c} with child birthweight and birthweight percentile. For all analyses, a two-tailed *p* value of 0.05 was considered significant. All statistical analyses were performed using the Statistical Package for Social Science (SPSS 14.0; Chicago, IL, USA).

Results

Islet autoantibody risk in relation to maternal and paternal type 1 diabetes A total of 63 children had a positive islet autoantibody outcome. Life table islet autoantibody frequencies were 5.5% (95% CI 3.5–7.5%) by 5 years in children of a father with type 1 diabetes and 3.2% (95% CI 2–4.4%) in children of a mother with type 1 diabetes (p= 0.04) (Fig. 1a). The difference in islet autoantibody

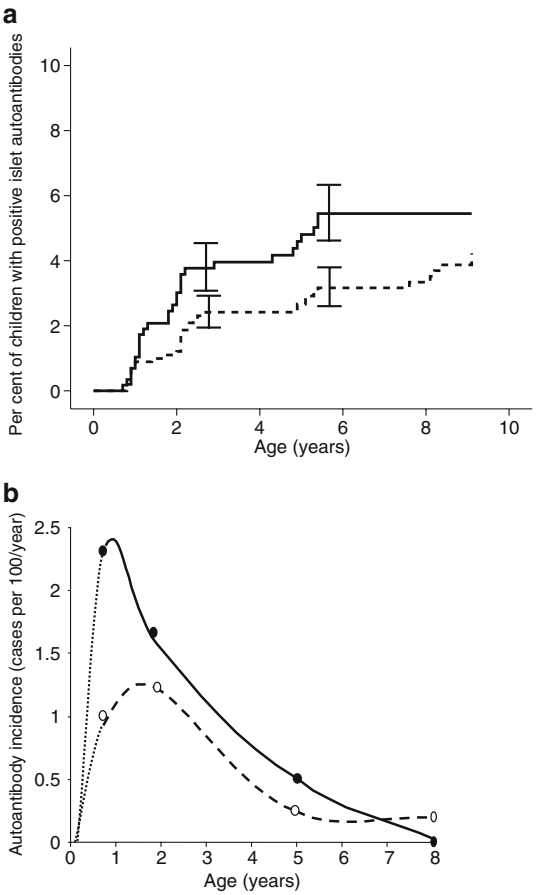

Fig. 1 Islet autoantibody development in BABYDIAB**. a** Life table analysis of islet autoantibodies in children of fathers with type 1 diabetes (solid line) compared with children of mothers with type 1 diabetes (dashed line) (p=0.026). **b** Islet autoantibody incidence (cases per 100/year) for children of fathers with type 1 diabetes (solid line) and children of mothers with type 1 diabetes (dashed line). Incidence is shown at the ages of islet autoantibody testing (9 months, 2 years, 5 years and 8 years). Error bars indicate SE of the cumulative risk. n=578, 522, 456 and 255 for the children of fathers with diabetes at 9 months, 2 years, 5 years and 8 years, respectively, and 1,008, 909, 791 and 552 for children of mothers with diabetes at 9 months, 2 years, 5 years and 8 years, respectively

incidence (new antibody events per year of follow-up) between children of mothers vs fathers with type 1 diabetes was most marked at the 9 month visit (Fig. 1b).

Factors associated with pregnancies in women with type 1 diabetes To identify potential factors that modify islet autoantibody risk, differences between children of mothers with type 1 diabetes and children of non-diabetic mothers were examined during gestation, delivery, and the first 9 months of life (Table 1). Differences were observed in gestational age (median 39 vs 40 weeks, $p<0.0001$) and the proportion of preterm deliveries (13.3 vs 4.9%, $p=0.0001$), birthweight (median 3,500 vs 3,410 g, $p=0.001$), the proportion of deliveries performed by Caesarean section (47.7 vs 19.3%, $p<0.0001$), Apgar score (10 min score <10: 30 vs 8.3%; $p=0.0001$), maternal age at delivery (29.6 vs 30.4 years, $p=0.002$) and the proportion of children breastfed (76.7 vs 87%, $p<0.0001$). No difference was observed for maternal smoking, weight gain during the first year of life, sex of the child, parity status, and the frequency of HLA DR4 alleles or *INS* VNTR genotypes in children.

Maternal type 1 diabetes-associated factors and islet autoantibody risk in children Factors that were associated with pregnancies of mothers with type 1 diabetes in this cohort were examined with respect to the risk of developing islet autoantibodies in the children from the total cohort using Cox proportional hazard analysis (Table 2). Islet autoantibody risk was significantly associated with birthweight ($p=0.004$; $p_{corrected}=0.032$). Compared with children whose birthweight was in the middle tertile, the frequencies of islet autoantibodies were reduced in children whose birthweight was in the lower (adjusted HR 0.43, $p=0.009$) or upper tertile (adjusted HR 0.44, $p=0.008$) of the study group. The significant association between birthweight and islet autoantibody risk was most evident in children of mothers with type 1 diabetes (Fig. 2a; Table 3). Associations in children of mothers with type 1 diabetes remained significant when birthweights were corrected for gestational age and expressed as *z* scores (5 year risks: 1.7% lowest tertile; 7.4% for middle tertile; 2.2% for highest tertile; $p=0.002$ lowest tertile vs middle tertile and highest tertile vs middle tertile). Preterm deliveries, Caesarean section, Apgar scores, maternal age, breastfeeding and weight gain within the first year of life were not significantly associated with islet autoantibody risk.

Maternal HbA_{1c} and islet autoantibody risk in the child Birthweight in children of mothers with type 1 diabetes was correlated with third trimester maternal HbA_{1c} ($r=0.43$, $p<10^{-10}$). Therefore, islet autoantibody risk in the children of mothers with type 1 diabetes was further examined after stratification for HbA_{1c} as high (>7%), moderately elevated (5.7–7%) and near normal (<5.7%; Table 3). Compared with 255 children born to mothers with near-normal HbA_{1c} (5 year risk 5.0%; 95% CI 2.2–7.8%), islet autoantibody risk in children was significantly reduced if mothers had moderately elevated HbA_{1c} (5 year risk 1.2%; 95% CI 0.1–2.6%; $p=0.035$; $n=262$), and increased if mothers had high HbA_{1c} values above (5 year risk 15.4%; 95% CI 4.8–26%; $p=0.022$; $n=50$). Both birthweight and maternal HbA_{1c} significantly affected the risk of development of islet autoantibodies in children in a multivariate model. Moreover, significance remained when HLA DR4 (previously found to be associated with birthweight in this cohort [27]) was included in the model (Table 3).

Discussion

The risk of type 1 diabetes is decreased in children of mothers with type 1 diabetes compared with children of fathers with type 1 diabetes. Here, we show that the

Table 2 Maternal diabetes associated factors and risk of islet autoantibodies in offspring

Parameter	Islet autoantibodies, no. positive (total)	Adjusted HR (95% CI)
Preterm delivery		$p=0.87$
No	55 (1,313)	1 (reference)
Yes	6 (147)	1.07 (0.46–2.52)
Birthweight		$p=0.004$; $p_c=0.032$
1st tertile (<3,250 g)	14 (485)	0.43 (0.23–0.81), $p=0.009$
2nd tertile (3,250–3,700 g)	33 (495)	1 (reference)
3rd tertile (>3,700 g)	14 (497)	0.42 (0.22–0.79), $p=0.007$
Caesarean section		0.67
No	38 (859)	1 (reference)
Yes	22 (509)	1.13 (0.65–1.95)
Apgar score at 5 min		$p=0.15$
10	22 (516)	1 (reference)
<10	8 (379)	0.55 (0.24–1.26)
Apgar score at 10 min		$p=0.91$
10	25 (706)	1 (reference)
<10	5 (187)	0.91 (0.34–2.46)
Breastfeeding		$p=0.75$
No	10 (286)	0.90 (0.45–1.78)
Yes	50 (1,171)	1 (reference)
Full breastfeeding ≥3 months		$p=0.5$
No	32 (730)	1.19 (0.71–2.00)
Yes	27 (683)	1 (reference)
Maternal age		$p=0.3$
1st tertile (14–28 years)	17 (523)	0.96 (0.50–1.85)
2nd tertile (28–31 years)	19 (524)	1 (reference)
3rd tertile (>31 years)	27 (520)	1.44 (0.80–2.59)

HRs were adjusted for maternal diabetes

p_c, $p_{corrected}$

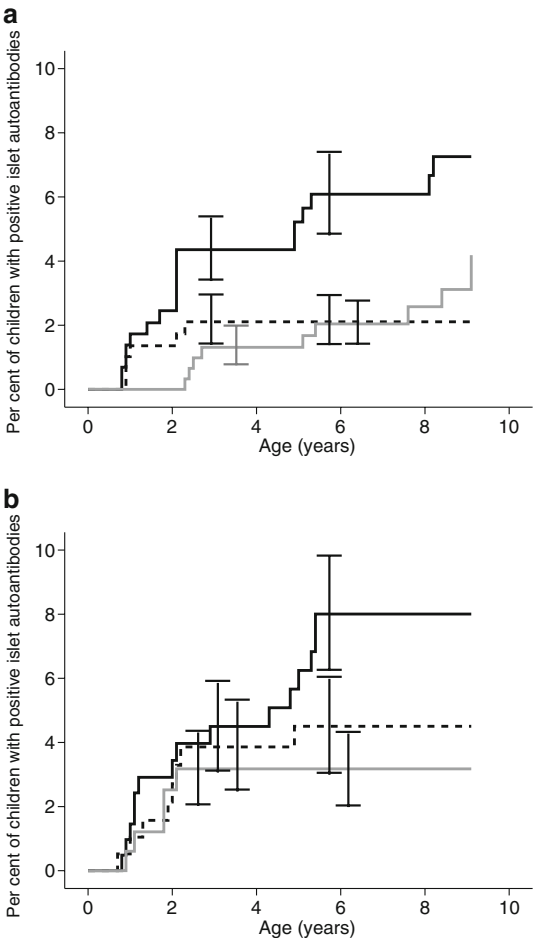

Fig. 2 Islet autoantibody frequency relative to child's birthweight stratified by birthweight tertiles (lowest tertile, dashed line; middle tertile, solid black line; highest tertile, solid grey line). Life table analysis of islet autoantibody risk in BABYDIAB children of mothers with type 1 diabetes (**a**) and children of fathers with type 1 diabetes (**b**). Error bars indicate SE of the cumulative risk. Differences were observed for children of mothers with type 1 diabetes: compared with children with birthweights in the middle tertile, islet autoantibody risk was decreased in children with birthweights in the lowest tertile (p=0.02) and children with birthweights in the highest tertile (p=0.01). n=294, 267, 232 and 151 for children in the lowest tertile; 289, 259, 223 and 163 in the middle tertile and 332, 307, 275 and 183 in the highest tertile at 9 months, 2 years, 5 years and 8 years, respectively, for children of mothers with type 1 diabetes (**a**). Corresponding numbers for children of fathers with type 1 diabetes (**b**) were 191, 172, 150 and 87 in the lowest tertile; 206, 185, 164 and 89 in the middle tertile; and 165, 151, 131 and 75 in the highest tertile

children of mothers with type 1 diabetes also have a reduced risk of developing islet autoantibodies, particularly in the first year of life. This provides a model to study factors that may be protective against the development of early islet autoimmunity. Among the factors studied, both low and high birthweights were found to be associated with protection against islet autoantibodies in children of mothers with type 1 diabetes.

The BABYDIAB Study is the largest and longest prospective study from birth of children of parents with type 1 diabetes. All children were singleton births, had one parent with type 1 diabetes and were born in Germany, and 98% have German parents [27], providing a relatively homogeneous study group. Although the number of cases with a positive outcome may be relatively small (n=63), all positive children developed multiple islet autoantibodies, which are known to be highly predictive of progression to type 1 diabetes [1, 19, 28]. The limitations of the cohort include that it is not population based and participation is on a voluntary basis. Therefore, it is possible that the families are not entirely representative of all children of parents with type 1 diabetes. With respect to the current analysis, there were relatively few missing values for most of the variables that were analysed, including birthweight. One exception was maternal HbA_{1c}, which was missing in over 40% of children born to mothers with type 1 diabetes. Moreover, HbA_{1c} measurements were performed locally using different assays and the association between maternal HbA_{1c} and islet autoantibody risk might have differed if they were measured centrally with a single method. Finally, there is co-linearity between some of the variables analysed, and some variables are likely to be influenced by other confounder variables such as socioeconomic status, education and maternal BMI that were not available for the analysis. Thus, observed associations could in some cases be secondary to other variables not available in this analysis.

Table 3 Islet autoantibody risks and Cox proportional hazards model (multivariate) for the influence of birthweight, maternal HbA_{1c} during pregnancy, and child HLA DR4 phenotype on islet autoantibody in children of mothers with type 1 diabetes

Variable	5 year risk (%) (95% CI)	No. of cases	Adjusted HR (95% CI)
Birthweight			p=0.023
1st tertile (<3,250 g)	2.1 (0.4–3.8)	6	0.34 (0.13–0.86); p=0.023
2nd tertile (3,250–3,700 g)	6.1 (3.2–9)	18	1 (reference)
3rd tertile (>3,700 g)	2.0 (0.3–3.7)	9	0.42 (0.19–0.95); p=0.037
HbA_{1c}			p=0.00009
<5.7% (n=255)	5.0 (2.2–7.8);	14	1 (reference)
5.7–7% (n=262)	1.2 (0.1–2.6)	6	0.35 (0.13–0.92) p=0.032
>7% (n=50)	15.4 (4.8–26)	7	2.76 (1.11–6.87), p=0.029
HLA *DRB1**04			p=0.0001
*DRB1*04* negative	0.9 (0.1–1.7)	5	1 (reference)
*DRB1*04* positive	6.1 (3.7–8.5)	28	6.5 (2.5–16.8); p=0.0001

The relatively marked reduction in the risk of developing islet autoantibodies found in children of mothers with type 1 diabetes is consistent with the established reduced diabetes risk in these children compared with children of fathers with type 1 diabetes [5–7] and an earlier cross-sectional study of islet autoantibody prevalence in children of parents with type 1 diabetes [29]. The reduced autoantibody risk appears to be specific for islet autoimmunity, since we saw no effect of maternal type 1 diabetes on the risk of transglutaminase autoantibodies (8 year risk 3.8% in children of mothers with type 1 diabetes vs 2.8% in children of fathers with type 1 diabetes; data not shown). Much of the difference in islet autoantibody risk was observed for antibody development in the first 2 years of life.

Numerous differences between children born to mothers with type 1 diabetes and children born to non-diabetic mothers were observed. Most were related to gestation, gestational growth and delivery and were consistent with previous reports [14–17, 30, 31]. Of these, birthweight was significantly associated with islet autoantibody risk and could, in part, explain the reduced islet autoantibody risk in children of mothers with type 1 diabetes. Both low and high birthweights were associated with reduced risk in children of mothers with type 1 diabetes. Associations were less evident in children of non-diabetic mothers. Whereas the findings with respect to low birthweight are consistent with a previous report showing a reduced risk of type 1 diabetes in children who were small for gestational age [32], high birthweight has not previously been shown to be associated with reduced type 1 diabetes risk. Interestingly, high birthweight in children of mothers with type 1 diabetes in our cohort was also protective for diabetes development (adjusted HR vs birthweight for the middle tertile 0.32; 95% CI 0.11–0.88; p=0.027; data not shown). Since high birthweight is associated with maternal HbA_{1c}, we performed a sub-analysis of the data stratifying for maternal HbA_{1c} (Electronic supplementary material [ESM] Fig. 1). This preliminary analysis indicated that moderately elevated maternal HbA_{1c}, found in about half the mothers with type 1 diabetes in this cohort, was independently associated with reduced risk of developing islet autoantibodies in the child. It is possible, therefore, that the inverted U-shaped islet autoantibody risk relationship with respect to birthweight observed in children of mothers with type 1 diabetes is because of a decreased risk conferred by low birthweight and a decreased risk conferred by moderately elevated maternal HbA_{1c}. With respect to maternal HbA_{1c}, it is important to note that risk reduction did not appear to be directly related to maternal glycaemic control, since high maternal HbA_{1c} (>7%), albeit found in relatively few mothers, was associated with a marked increase in islet autoantibody risk.

The current findings complement our previous report, which showed protection against islet autoantibodies and diabetes development by maternal transfer of islet autoantibodies [33]. Although we cannot provide insight into mechanisms of protection, it is tempting to interpret the associations of autoantibody transfer, high birthweight and increased glucose with reduced risk of islet autoimmunity as reflecting increased immune tolerance to islet antigens during fetal and newborn life. Regardless of the mechanisms, our findings, although preliminary and restricted to offspring of mothers with type 1 diabetes, are inconsistent with hypotheses suggesting that increased metabolic demand through increased weight or insulin resistance or rapid growth periods as seen in children with low birthweight can increase the risk of developing islet autoimmunity [34–39].

In conclusion, we suggest that the reduced islet autoantibody risk during early infancy caused through a maternal type 1 diabetes environment may help understanding of pathophysiological modes of immunomodulation, which could eventually help reduce the incidence of type 1 diabetes in childhood.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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