Early infant growth is associated with the risk of islet autoimmunity in genetically susceptible children

Andreas Beyerlein [1*] , Elisabeth Thiering[2*], Maren Pflueger [1], Martin Bidlingmaier [3], Joanna Stock[1,4], Annette Knopff[1,4], Christiane Winkler [1,4], Joachim Heinrich [2], Anette-Gabriele Ziegler [1,4]

1. Institute of Diabetes Research, Helmholtz Zentrum München, and Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München, Ingolstaedter Landstrasse 1, 85764, Neuherberg, Germany
2. Institute of Epidemiology I, Helmholtz Zentrum München, Ingolstaedter Landstr. 1, 85764 Neuherberg, Deutschland
3. Endocrine Research Unit, Medizinische Klinik und Poliklinik IV, LMU München, Ziemssenstrasse 1, 80336 Munich, Germany
4. Forschergruppe Diabetes e.V., Ingolstaedter Landstrasse 1, 85764, Neuherberg, Germany

*equal contribution to this study

Prof. Dr. med. Anette-Gabriele Ziegler
Institute of Diabetes Research,
Helmholtz Zentrum München
Ingolstaedter Landstr. 1
85764 Neuherberg, Germany
Email: anziegler@lrz.uni-muenchen.de
Tel: +49 89 3187 2896
Fax: +49 89 3187 3144

Word count: 4616

Tables: 5

Figures: 1

Running title: Early growth and islet autoimmunity

Abbreviations:

GAD65	Glutamic acid decarboxylase 65
HLA	Human leukocyte antigen
IGF-1	Insulin-like growth factor 1
IGF-BP3	Insulin-Like Growth Factor Binding Protein 3
IA-2	Insulinoma-associated antigen-2
Zn-T8	Zinc transporter 8

Abstract

Background: Islet autoimmunity commonly develops early in infancy. We assessed whether specific parameters of early growth (including weight gain) were associated with the development of islet autoimmunity in children of type 1 diabetes patients, taking individual developmental patterns into account.

Methods: Growth parameters were estimated in n=1011 children followed from birth in the prospective BABYDIAB and BABYDIET studies using longitudinal models. Cox proportional hazard models, adjusted for study, sex, gestational age, birth weight percentile and maternal type 1 diabetes status, were calculated to assess hazard ratios (HR) for islet autoimmunity with corresponding 95% confidence intervals (95% CI) by 2 SD increases in growth parameters. In a subset of n=170 infants, we investigated whether the growth hormones IGF-1 and IGFBP-3 were in the causal pathway.

Results: We found an early age at infant BMI peak to be associated with the development of islet autoimmunity (HR 0.60 (95% CI 0.41-0.87), per 2 SD increase in age). Islet autoimmunity was also associated with BMI difference between infant BMI peak and childhood BMI rebound (HR 1.52 (95% CI 1.04-2.22)), but not after adjustment for age at infant BMI peak, and not with other parameters such as peak height and weight velocity during infancy. Serum concentrations of IGF-1 and IGFBP-3 at birth, 9 months and 2 years, respectively, were not significantly different between children with and without later islet autoimmunity.

Conclusions: Variations in early growth rate have subtle effects on the risk of islet autoimmunity with growth hormones unlikely to be in the causal pathway.

Keywords: Islet autoimmunity, infant growth, Insulin-like growth factor 1

Introduction

Type 1 diabetes is one of the most common chronic diseases in childhood, and its incidence is rising worldwide with highest increases in young children (1). The disease is preceded by a preclinical period of islet autoimmunity leading to the dysfunction and destruction of pancreatic beta cells. Islet autoimmunity most commonly develops early in infancy with a peak incidence around 1 to 2 years of age (2, 3). Therefore, factors that affect islet beta cells or immune response to beta cells in the first year of life are likely to be important for programming the initiation of islet autoimmunity (4, 5).

The development of type 1 diabetes is clearly environmentally induced (6), but specific causes remain to be determined. According to the accelerator hypothesis (7), early growth and weight gain are potential candidates, as the rates of both have been increasing worldwide in recent decades (8-13). In a previous analysis, we had focused on weight and body mass index (BMI) after the age of 2 years and found no difference between children who developed islet autoimmunity and those remaining autoantibody-negative (14). Several other studies reported associations between growth and type 1 diabetes risk (15-23), but detailed data on the relationship between islet autoimmunity and growth within the first year of life is scarce. Furthermore, comparing height, weight or BMI between a priori defined time points as done in these studies does not take into account that early developmental patterns may differ considerably between individuals (24). Here we use a more elaborate approach, assessing age and BMI at infant BMI peak and childhood BMI rebound, which denote the maximum and minimum of a child's individual BMI trajectory, respectively (25). Additionally, we calculated peak height and weight velocity in early life, which have already been shown to be associated with asthma (26), later BMI (27, 28) and blood pressure (29). We assessed whether these parameters of early growth – including weight gain – were associated with the development of islet autoimmunity using data from two prospective studies including up to five height / weight measurements within the first year of life. Further, we were able to

examine the potential role of two growth hormones, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) (30), in the causal pathway.

Methods

Study population

Data from two ongoing German birth cohorts of healthy neonates with a genetically increased risk born between 1989 and 2006 (BABYDIAB, BABYDIET) were combined for longitudinal analyses of islet autoimmunity and type 1 diabetes. The BABYDIAB study examines the natural history of islet autoimmunity and type 1 diabetes in children born to a mother or a father with type 1 diabetes. Recruitment began in 1989 and ended in 2000. In the BABYDIET study, 150 newborns with a first degree relative with type 1 diabetes and with type 1 diabetes risk HLA genotypes were randomized to gluten exposure at 6 or 12 months of age between 2000 and 2006. The intervention had no effect on islet autoimmunity outcome or on growth parameters (31). For both studies, a detailed description of the study design has been reported previously (31-33). The studies were approved by the ethical committee of Bavaria, Germany (Bayerische Landesärztekammer No. 95357 and Ludwig-Maximilians University No. 329/00 respectively). All families gave written informed consent to participate in the study. Investigations were carried out in accordance with the principles of the Declaration of Helsinki, as revised in 2000.

Growth measurements

Length or height and weight measurements during infancy were obtained by pediatricians or general practitioners performing the examinations of the well-baby preventive health program offered to all children in Germany (‘U-Untersuchungen’). These are regularly conducted at birth and at the age of 3-10 days, 4-6 weeks and 3-4, 6-7, 10-12, 21-24, 46-48 and 60-64 months. Thereafter, data on height and weight was assessed during study visits in three year

intervals in the BABYDIAB study and yearly in the BABYDIET study. Length of children below the age of 2 years was measured with an infantometer with a precision of ± 1 mm and height of children older than 2 years with a stadiometer with a precision of ± 1 mm. Weight was measured digitally or beam using a scale with a precision of ± 100 g. Sex and gestational age specific birth weight percentiles were calculated based on German reference values (34) and used to define small and large for gestational age status (<10^{th} and >90^{th} percentile, respectively).

Peak weight and peak height velocity

Height and weight growth curves for each individual based on their longitudinal growth data through age 2 years were calculated using the Reed1 model (35), which is a modification of the original Reed model (36) and was previously applied in epidemiological studies (26, 27, 29). All available anthropometric measurements from birth until the age of 2 years were used; infants with fewer than 3 growth measurements and also twins were excluded from all analyses, yielding a sample size of n=1011. Growth curves were computed separately for boys and girls using nonlinear mixed models with a random effects term for each person. For each individual the first derivative of the best linear unbiased prediction (BLUP) of the growth curve was used to obtain growth velocity curves between birth and the age of 2 years. Peak height velocity and peak weight velocity were defined as the maximum of the respective growth velocity curves, respectively.

Age and BMI at infant BMI peak and childhood BMI rebound

The shape of the typical BMI curve is irregular and thus modeling and interpretation of individual longitudinal BMI curves of the entire life span is complex (37). We focused our analysis on age and BMI at infant BMI peak and childhood BMI rebound, as well as the difference in age and BMI between those milestones. BMI measurements were modeled in a

piecewise fashion as previously described (38). Measurements in the age window 2 weeks to 18 months were used to model BMI curves around the timing of infant BMI peak, and BMI measurements between age 18 months and 13 years for childhood BMI rebound using mixed models (25, 26). Children with fewer than three measurements per age window were excluded from this analysis. Gender adjusted mixed models with random intercept and random slope for each individual and with a linear, quadratic and cubic effect of age to account for nonlinearity of BMI change over time were applied to fit the individual log-transformed BMI curve for every child (38). Subsequently, age and BMI at infant BMI peak and childhood BMI rebound were derived as maximum and minimum of the individual BMI curve (25, 26).

Outcome variables

Islet autoantibodies were measured in venous blood samples from scheduled visits. Children in the BABYDIAB study had scheduled visits at birth, and at age 9 months, and at 2, 5, 8, 11, 14, 17 and 20 years of age, whereas children in the BABYDIET study had 3-monthly visits from birth until the age of 3 years, and yearly until the age of 12 years. Measurement of islet autoantibodies has been described elsewhere (33, 39). Islet autoimmunity was defined by the development of persistent autoantibodies to one or more of the antigens insulin, GAD65, IA-2 or Zn-T8, and multiple islet autoimmunity by the presence of persistent autoantibodies to more than one of the antigens. Samples with values above the 99th percentile of control children were defined as positive. Persistence was defined as positive in at least two consecutive samples and in the last available sample. Islet autoantibody assays were evaluated by the Diabetes Autoantibody Standardization Program (40).

Determination of IGF-1 and IGFBP-3 concentration

Serum IGF-1 and IGFBP-3 concentrations were determined at birth and at the age of 9 months and 2 years in a subset of the children. The analysis was restricted to samples never

defrosted, including 74 children who developed islet autoantibodies during follow-up (29 samples at birth, 46 samples at age 9 months, 15 samples at age 2 years) and 96 randomly selected children who remained islet autoantibody negative (48 samples at birth, 51 samples at age 9 months, 15 samples at age 2 years). IGF-1 and IGFBP-3 concentrations were determined by an automated chemiluminescence assay (iSYS, IDS) according to the manufacturer's instructions. The lower limit of quantification of the assays was 10ng/ml for IGF-1 and 80ng/ml for IGFBP-3.

Statistical analysis

Associations between growth parameters and the development of islet autoimmunity were analyzed by Cox proportional hazards regression. Hazard Ratios (HR) with corresponding 95% confidence intervals (95% CI) were estimated for 2 standard deviations (SD) increases in growth parameters. All models were calculated without inclusion of covariates (unadjusted) as well as adjusted for study (using random effects), sex, gestational age, birth weight percentile and maternal type 1 diabetes status. As information about breastfeeding was missing in 103 subjects, we adjusted for breastfeeding in a sensitivity analysis only. No adjustment was made for HLA risk, as this would have violated the proportional hazards assumption of the Cox regression models. Growth parameters of children were also compared relative to the presence of HLA risk genotypes as defined by the TEDDY study (41). In a sensitivity analysis for parameters in the period before infant BMI peak, we excluded children who developed islet autoimmunity before age 18 months to avoid backward causation. In another sensitivity analysis, models of growth parameters after infant BMI peak were additionally adjusted for age at infant BMI peak.

Levels of IGF-1 and IGFBP-3 at 9 months were correlated with the age of infant BMI peak and compared between children with and without later islet autoimmunity using the Mann-Whitney U test. Linear regression was used to adjust the association between islet

autoimmunity and IGF1 / IGFBP-3 by maternal type 1 diabetes status, sex, cesarean section and weight for gestational age status. Statistical significance was determined by an alpha-level of 0.05.

Results

Growth

Growth indices were calculated from 1011 children (Table 1). Distinct growth phases could be discerned with infant BMI peak occurring on average at 9 months of age and childhood BMI rebound at 5 years (Figure 1).

Overall, peak growth velocity was higher in boys compared to girls, and boys had higher BMI values at infant BMI peak and childhood BMI rebound (Table 2). Maternal type 1 diabetes during pregnancy, weight for gestational age status, and HLA risk status were also significantly associated with infant growth. Breastfeeding of three months or more was associated with lower peak height and weight velocity, but not with other growth parameters (data not shown).

Within the initial period of increasing BMI, an early age at infant BMI peak was significantly associated with development of islet autoantibodies (any islet autoantibodies: unadjusted HR 0.64 (95% CI 0.45-0.91) and multiple islet autoantibodies: unadjusted HR 0.59 (95% CI 0.37-0.95) per 2 SD increase in age; Table 3). The associations remained significant after adjustment for sex, maternal type 1 diabetes status and weight for gestational age status (any islet autoantibodies: adjusted HR 0.60 (95% CI 0.41-0.87) and multiple islet autoantibodies: adjusted HR 0.54 (95% CI 0.33-0.89) per 2 SD increase in age). Peak weight velocity, peak height velocity and BMI at infant BMI peak were not significantly associated with islet autoimmunity risk. The results were similar if children who developed islet autoimmunity before age 18 months were excluded (data not shown).

Examining parameters within the following BMI decrease period, islet autoimmunity risk was positively associated with BMI difference between infant BMI peak and childhood BMI rebound (any islet autoantibodies: adjusted HR 1.52 (95% CI 1.04-2.22); multiple islet autoantibodies: adjusted HR 2.08 (95% CI 1.23-3.51) per 2 SD difference, Table 3), but not with BMI or age at childhood BMI rebound. After additional adjustment for age at infant BMI peak, BMI difference between infant BMI peak and childhood BMI rebound was not significantly associated with islet autoimmunity risk any more (adjusted HR 1.16 (95% CI 0.76-1.75)). The two growth parameters were inversely correlated with each other (Pearson's r=-0.50).

Additional adjustment for breastfeeding yielded almost identical results (data not shown).

IGF-1 and IGFBP-3

Age at infant BMI peak was significantly correlated with IGF-1 (r=0.25, *P*=0.01), but not with IGFBP-3 (r=0.03, *P*=0.77) at 9 months. However, serum concentrations of IGF-1 and IGFBP-3 at birth, 9 months and 2 years, respectively, were not significantly different between children who developed islet autoantibodies and children who remained islet autoantibody negative in unadjusted and adjusted analyses (tables 4 and 5).

Discussion

Variations in growth and growth signaling molecules have been previously associated with type 1 diabetes but detailed data on the relationship between islet autoimmunity and growth within the first year of life is scarce. We investigated growth parameters in early infancy and observed that early age of infant BMI peak and high BMI difference between infant BMI peak and childhood BMI rebound were associated with increased risk of islet autoimmunity, while other growth parameters including peak height and peak weight velocity were not. However, early age at infant BMI peak was associated with higher BMI difference between

infant BMI peak and childhood BMI rebound and did partly explain the association of the latter parameter with islet autoimmunity.

The change in BMI during early infancy (figure 1) is remarkably similar to the change in incidence of islet autoimmunity during this period (2, 3). It is likely that body composition changes influence beta cell activity and thus indirectly modify risk of islet autoimmunity. Supporting this notion, we found subtle differences in children who developed islet autoantibodies, potentially indicating that children have a higher type 1 diabetes risk if their body begins to stretch early and / or if they have a pronounced childhood BMI rebound.

Our findings are novel since longitudinal modeling of infant growth in the first years of life has not been reported in children who develop islet autoimmunity. Added to previous reports of higher weight or height velocities in children developing islet autoimmunity, there is now a growing body of evidence that growth demands on the beta cell influence the risk of islet autoimmunity. This influence appears to be minor, however, and it is unknown whether it can be extrinsically modified by, for example, diet.

The rationale to use differences of 2 SD for each growth parameter, as was done in most previous studies on this topic (27-29), was to make changes in these parameters comparable to each other. Although the magnitude of the differences between islet autoantibody positive and negative children is insufficient to impact risk assessment, they do provide clues to possible pathogenetic mechanisms. IGF-1 is an important anti-apoptotic factor, regulates beta cell growth and survival, and IGF-1 replacement therapies delay onset of autoimmune diabetes in these models (42). A decrease in IGF-1 concentration after birth may, therefore, be of relevance to the heightened risk of islet autoantibody seroconversion seen between 6 and 24 months of age (2, 3). We therefore examined whether children who developed islet autoimmunity differed in IGF-1 and IGFBP-3 concentrations at birth and around the time of the infant BMI peak. IGF-1 concentrations were associated with the age of the infant BMI peak and were lower in samples at age 9 months compared to birth suggesting that there is an

evident relationship between growth velocity parameters and growth signalling molecules. However, concentrations of both hormones were similar between children with and without later islet autoimmunity. Thus it seems rather questionable that these growth hormones are in the causal pathway between early growth / weight gain and islet autoimmunity, although we cannot exclude that the statistical power of these analyses was too low to detect significant differences, as these could be performed in only 170 of the 1011 children. The fact that we had to exclude a large number of children from our analyses because they had fewer than three growth measurements might be another potential drawback of this study. Further, considering the relatively low number of events (n=135), we cannot preclude that we missed associations of islet autoimmunity risk with certain growth parameters due to insufficient statistical power. It might further be argued that parameters such as peak height and weight velocity could be too imprecise in general to find meaningful associations with the sample size of the underlying data. However, in a dataset of a similar size, significant associations of these growth parameters have been detected with respect to blood pressure measurements in 10-year old children (29). It is also unclear whether these findings in genetically high-risk children can be generalized to infants in the general population. However, it appears practically impossible to conduct such a prospectively designed study with frequent measurement of islet autoantibodies in a general population setting.

In conclusion, our study demonstrates that the risk to develop islet autoimmunity is subtly affected by early growth, with growth hormones unlikely to be in the causal pathway.

Acknowledgement We thank Marlon Scholz, Anita Gavrisan (Forschergruppe Diabetes e.V. at Helmholtz Zentrum) for data collection and expert technical assistance, and Ramona Puff (Klinikum Rechts der Isar, Technische Universität München) for laboratory management. We

also thank all paediatricians and family doctors in Germany for participating in the BABYDIAB Study.

Funding The study was supported by grants from the Juvenile Diabetes Research Foundation (JDRF 17-2012-16 and 1-2006-665), the Helmholtz Zentrum München, the Competence Network for Diabetes Mellitus funded by the Federal Ministry of Education and Research (FKZ 01GI0805-07), the German Center for Diabetes Research (DZD), the European Union (EP7- HEALTH-2007, DIAPREPP N202013), and the Juvenile Diabetes Research Foundation.

Duality of interest We declare that we have no conflict of interest.

Contribution statement MP and ET acquired and reviewed data, undertook statistical analysis, interpreted results, and drafted the manuscript. AB contributed to statistical analyses and to the first and subsequent drafts of the manuscript. JS, AK and CW assisted in follow-up and obtaining data, undertook analysis, and critically reviewed the manuscript for intellectual content. MB measured IGF-1 and IGFBP-3 and critically reviewed the manuscript for intellectual content. JH contributed to statistical analyses, interpreted the results, and critically reviewed the manuscript for intellectual content. A-GZ is the principal investigator of the BABYIAB and BABYDIET studies, designed the studies and concept, undertook statistical analyses, interpreted the results, wrote the manuscript and critically reviewed it for intellectual content.

References

1. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G, Group ES. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet. 2009; 373:2027-33.

2. Parikka V, Nanto-Salonen K, Saarinen M, Simell T, Ilonen J, Hyoty H, et al. Early seroconversion and rapidly increasing autoantibody concentrations predict prepubertal manifestation of type 1 diabetes in children at genetic risk. Diabetologia. 2012; 55:1926-36.

3. Ziegler AG, Bonifacio E, Babydiab-Babydiet Study Group. Age-related islet autoantibody incidence in offspring of patients with type 1 diabetes. Diabetologia. 2012; 55:1937-43.

4. Knip M, Veijola R, Virtanen SM, Hyoty H, Vaarala O, Akerblom HK. Environmental triggers and determinants of type 1 diabetes. Diabetes. 2005; 54 Suppl 2:S125-36.

5. Vehik K, Dabelea D. The changing epidemiology of type 1 diabetes: why is it going through the roof? Diabetes/metabolism research and reviews. 2011; 27:3-13.

6. Akerblom HK, Vaarala O, Hyoty H, Ilonen J, Knip M. Environmental factors in the etiology of type 1 diabetes. American journal of medical genetics. 2002; 115:18-29.

7. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. Diabetologia. 2001; 44:914-22.

8. Smith SM, Craig LC, Raja AE, McNeill G, Turner SW. Growing up before growing out: secular trends in height, weight and obesity in 5--6-year-old children born between 1970 and 2006. Archives of disease in childhood. 2013; 98:269-73.

9. Rao S, Kanade AN, Joshi SB, Sarode JS. Secular trends in growth of preschool children from rural Maharashtra, India. Journal of health, population, and nutrition. 2012; 30:420-30.

10. Chen TJ, Ji CY. Secular change in stature of urban Chinese children and adolescents, 1985-2010. Biomedical and environmental sciences : BES. 2013; 26:13-22.

11. Marques-Vidal P, Madeleine G, Romain S, Gabriel A, Bovet P. Secular trends in height and weight among children and adolescents of the Seychelles, 1956-2006. BMC public health. 2008; 8:166.

12. Freedman DS, Khan LK, Serdula MK, Ogden CL, Dietz WH. Racial and ethnic differences in secular trends for childhood BMI, weight, and height. Obesity (Silver Spring). 2006; 14:301-8.

13. Freedman DS, Khan LK, Serdula MK, Srinivasan SR, Berenson GS. Secular trends in height among children during 2 decades: The Bogalusa Heart Study. Archives of pediatrics & adolescent medicine. 2000; 154:155-61.

14. Winkler C, Marienfeld S, Zwilling M, Bonifacio E, Ziegler AG. Is islet autoimmunity related to insulin sensitivity or body weight in children of parents with type 1 diabetes? Diabetologia. 2009; 52:2072-8.

15. Larsson HE, Hansson G, Carlsson A, Cederwall E, Jonsson B, Jonsson B, et al. Children developing type 1 diabetes before 6 years of age have increased linear growth independent of HLA genotypes. Diabetologia. 2008; 51:1623-30.

16. Dabelea D, D'Agostino RB, Jr., Mayer-Davis EJ, Pettitt DJ, Imperatore G, Dolan LM, et al. Testing the accelerator hypothesis: body size, beta-cell function, and age at onset of type 1 (autoimmune) diabetes. Diabetes care. 2006; 29:290-4.

17. Knerr I, Wolf J, Reinehr T, Stachow R, Grabert M, Schober E, et al. The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9,248 German and Austrian children with type 1 diabetes mellitus. Diabetologia. 2005; 48:2501-4.

18. Blom L, Persson LA, Dahlquist G. A high linear growth is associated with an increased risk of childhood diabetes mellitus. Diabetologia. 1992; 35:528-33.

19. Johansson C, Samuelsson U, Ludvigsson J. A high weight gain early in life is associated with an increased risk of type 1 (insulin-dependent) diabetes mellitus. Diabetologia. 1994; 37:91-4.

20. Eurodiab Substudy 2 Study Group. Rapid early growth is associated with increased risk of childhood type 1 diabetes in various European populations. Diabetes care. 2002; 25:1755-60.

21. Lamb MM, Yin X, Zerbe GO, Klingensmith GJ, Dabelea D, Fingerlin TE, et al. Height growth velocity, islet autoimmunity and type 1 diabetes development: the Diabetes Autoimmunity Study in the Young. Diabetologia. 2009; 52:2064-71.

22. Couper JJ, Beresford S, Hirte C, Baghurst PA, Pollard A, Tait BD, et al. Weight gain in early life predicts risk of islet autoimmunity in children with a first-degree relative with type 1 diabetes. Diabetes care. 2009; 32:94-9.

23. Bruining GJ. Association between infant growth before onset of juvenile type-1 diabetes and autoantibodies to IA-2. Netherlands Kolibrie study group of childhood diabetes. Lancet. 2000; 356:655-6.

24. Li C, Goran MI, Kaur H, Nollen N, Ahluwalia JS. Developmental trajectories of overweight during childhood: role of early life factors. Obesity (Silver Spring). 2007; 15:760-71.

25. Wen X, Kleinman K, Gillman MW, Rifas-Shiman SL, Taveras EM. Childhood body mass index trajectories: modeling, characterizing, pairwise correlations and socio-demographic predictors of trajectory characteristics. BMC medical research methodology. 2012; 12:38.

26. Flexeder C, Thiering E, Bruske I, Koletzko S, Bauer CP, Wichmann HE, et al. Growth velocity during infancy and onset of asthma in school-aged children. Allergy. 2012; 67:257-64.

27. Tzoulaki I, Sovio U, Pillas D, Hartikainen AL, Pouta A, Laitinen J, et al. Relation of immediate postnatal growth with obesity and related metabolic risk factors in adulthood: the northern Finland birth cohort 1966 study. American journal of epidemiology. 2010; 171:989-98.

28. Sovio U, Kaakinen M, Tzoulaki I, Das S, Ruokonen A, Pouta A, et al. How do changes in body mass index in infancy and childhood associate with cardiometabolic profile in adulthood? Findings from the Northern Finland Birth Cohort 1966 Study. Int J Obes (Lond). 2013.

29. Thiering E, Bruske I, Kratzsch J, Hoffmann B, Herbarth O, von Berg A, et al. Peak growth velocity in infancy is positively associated with blood pressure in school-aged children. Journal of hypertension. 2012; 30:1114-21.

30. Kelley KM, Oh Y, Gargosky SE, Gucev Z, Matsumoto T, Hwa V, et al. Insulin-like growth factor-binding proteins (IGFBPs) and their regulatory dynamics. The international journal of biochemistry & cell biology. 1996; 28:619-37.

31. Hummel S, Pflüger M, Hummel M, Bonifacio E, Ziegler AG. Primary dietary intervention study to reduce the risk of islet autoimmunity in children at increased risk for type 1 diabetes: the BABYDIET study. Diabetes care. 2011; 34:1301-5.

32. Hummel M, Bonifacio E, Schmid S, Walter M, Knopff A, Ziegler AG. Brief communication: early appearance of islet autoantibodies predicts childhood type 1 diabetes in offspring of diabetic parents. Annals of internal medicine. 2004; 140:882-6.

33. Ziegler AG, Hummel M, Schenker M, Bonifacio E. Autoantibody appearance and risk for development of childhood diabetes in offspring of parents with type 1 diabetes: the 2-year analysis of the German BABYDIAB Study. Diabetes. 1999; 48:460-8.

34. Voigt M, Schneider KT, Jahrig K. [Analysis of a 1992 birth sample in Germany. 1: New percentile values of the body weight of newborn infants]. Geburtshilfe Frauenheilkd. 1996; 56:550-8.

35. Simondon KB, Simondon F, Delpeuch F, Cornu A. Comparative study of five growth models applied to weight data from congolese infants between birth and 13 months of age. American Journal of Human Biology. 1992; 4:327-35.

36. Berkey CS, Reed RB. A model for describing normal and abnormal growth in early childhood. Human biology. 1987; 59:973-87.

37. Mayr A, Hothorn T, Fenske N. Prediction intervals for future BMI values of individual children: a non-parametric approach by quantile boosting. BMC medical research methodology. 2012; 12:6.

38. Sovio U, Mook-Kanamori DO, Warrington NM, Lawrence R, Briollais L, Palmer CN, et al. Association between common variation at the FTO locus and changes in body mass index from infancy to late childhood: the complex nature of genetic association through growth and development. PLoS genetics. 2011; 7:e1001307.

39. Achenbach P, Lampasona V, Landherr U, Koczwara K, Krause S, Grallert H, et al. Autoantibodies to zinc transporter 8 and SLC30A8 genotype stratify type 1 diabetes risk. Diabetologia. 2009; 52:1881-8.

40. Schlosser M, Mueller PW, Torn C, Bonifacio E, Bingley PJ, Participating L. Diabetes Antibody Standardization Program: evaluation of assays for insulin autoantibodies. Diabetologia. 2010; 53:2611-20.

41. Teddy Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY) study: study design. Pediatric diabetes. 2007; 8:286-98.

42. Chen W, Salojin KV, Mi QS, Grattan M, Meagher TC, Zucker P, et al. Insulin-like growth factor (IGF)-I/IGF-binding protein-3 complex: therapeutic efficacy and mechanism of protection against type 1 diabetes. Endocrinology. 2004; 145:627-38.

Table 1. Characteristics of N=1011 study subjects with at least one of the growth indices peak weight velocity, peak height velocity, infant BMI peak (BMIP), childhood BMI rebound (BMIR) determined. Percentages refer to non-missing values.

	Mean (SD) or n (%)
Follow-up in years	14.2 (3.8)
Peak weight velocity in kg/year	12.0 (2.2)
Peak height velocity in cm/year	45.9 (8.0)
Infant BMI peak (BMIP)	
BMI at BMIP in kg/m^2	17.0 (1.1)
Age at BMIP in months	8.9 (0.6)
Childhood BMI rebound (BMIR)	
BMI at BMIR in kg/m^2	15.4 (1.1)
Age at BMIR in years	5.2 (1.0)
Gender	
Male	507 (50.1 %)
Female	504 (49.9 %)
HLA	
low and medium risk	680 (67.9 %)
high risk	321 (32.1 %)
Gestational age in weeks	38.8 (1.8)
Birth weight percentiles	56.8 (30.7)
Weight for gestational age status	
small for gestational age (SGA)	91 (9.1 %)
appropriate for gestational age (AGA)	706 (70.8 %)
large for gestational age (LGA)	200 (20.1 %)
Maternal type 1 diabetes status	
Yes	602 (59.5 %)
No	409 (40.5 %)
Breastfeeding	
≥ 3 months	605 (66.6 %)
< 3 months	168 (18.5 %)
No	135 (14.9 %)
Any islet autoantibodies	135 (13.4 %)
Multiple islet autoantibodies	75 (7.8 %)
Type 1 Diabetes	46 (4.5 %)
Development of autoimmunity in years	5.4 (4.0)

Table 2. Mean (SD) of growth indices stratified by study characteristics

	Gender		Maternal type 1 diabetes status		HLA risk		Weight for gestational age status		
	male	female	yes	no	normal	high	SGA	AGA	LGA
Peak weight velocity	13.1[a] (1.9)	10.9[a] (1.9)	12.0 (2.2)	12.1 (2.2)	12.1[a] (2.2)	11.8[a] (2.1)	12.2 (1.9)	12.0 (2.1)	11.8 (2.4)
Peak height velocity	48.0[a] (7.6)	43.8[a] (7.9)	46.3[a] (8.5)	45.3[a] (7.2)	46.4[a] (8.2)	44.8[a] (7.6)	50.8[b] (8.0)	46.3[b] (7.7)	42.5[b] (7.6)
Infant BMI peak (BMIP)									
BMI at BMIP	17.3[a] (1.1)	16.7[a] (1.1)	17.1[a] (1.1)	16.9[a] (1.1)	17.0 (1.1)	17.0 (1.1)	16.5[b] (1.1)	16.9[b] (1.1)	17.6[b] (1.1)
Age at BMIP (months)	8.8 (0.6)	8.9 (0.6)	8.8[a] (0.6)	8.9[a] (0.6)	8.9 (0.6)	8.9 (0.6)	9.1[b] (0.6)	8.9[b] (0.6)	8.7[b] (0.5)
Childhood BMI rebound (BMIR)									
BMI at BMIR	15.5[a] (1.1)	15.3[a] (1.1)	15.5[a] (1.1)	15.3[a] (1.1)	15.4 (1.1)	15.4 (1.1)	15.0[b] (1.1)	15.3[b] (1.1)	15.9[b] (1.1)
Age at BMIR (years)	5.3 (1.0)	5.2 (1.0)	5.2 (1.1)	5.3 (1.0)	5.2 (1.1)	5.3 (1.0)	5.3[b] (1.1)	5.3[b] (1.0)	5.0[b] (1.1)
Difference BMIP and BMIR									
BMI difference	1.8[a] (1.0)	1.4[a] (1.0)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)	1.7 (0.9)	1.5 (1.1)	1.6 (1.0)	1.6 (1.0)
Age difference (years)	4.5 (1.0)	4.5 (1.0)	4.5 (1.0)	4.6 (1.0)	4.5 (1.0)	4.5 (1.0)	4.6[b] (1.1)	4.6[b] (1.0)	4.3[b] (1.0)

[a] P-value of t-Test <0.05 [b]P-value from ANOVA <0.05

Table 3. Hazard rates (HR) for risk of islet autoimmunity by early growth parameters (one per model) with and without adjustment for study (random effect), gender, gestational age, birth weight percentile and maternal type 1 diabetes status.

	Any islet autoantibodies				Multiple islet autoantibodies			
	Unadjusted HR[a] (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*	Unadjusted HR[a] (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*
Peak weight velocity	0.95 (0.68-1.33)	0.767	1.01 (0.68-1.51)	0.950	1.18 (0.75-2.13)	0.466	1.38 (0.82-2.34)	0.230
Peak height velocity	1.00 (0.71-1.40)	0.982	1.07 (0.70-1.62)	0.760	0.84 (0.52-1.35)	0.471	0.84 (0.47-1.52)	0.580
Infant BMI peak (BMIP)								
BMI at BMIP	1.03 (0.73-1.44)	0.871	1.07 (0.73-1.56)	0.740	1.37 (0.87-2.15)	0.176	1.47 (0.89-2.44)	0.130
Age at BMIP	0.64 (0.45-0.91)	0.013	0.60 (0.41-0.87)	0.007	0.59 (0.37-0.95)	0.029	0.54 (0.33-0.89)	0.016
Childhood BMI rebound (BMIR)								
BMI at BMIR	0.78 (0.55-1.13)	0.192	0.76 (0.52-1.12)	0.160	0.81 (0.49-1.32)	0.397	0.76 (0.45-1.28)	0.300
Age at BMIR	1.07 (0.75-1.52)	0.720	1.12 (0.78-1.62)	0.530	1.18 (0.73-1.90)	0.509	1.30 (0.79-2.15)	0.300
Difference BMIP and BMIR								
BMI difference	1.44 (1.00-2.07)	0.049	1.52 (1.04-2.22)	0.032	1.87 (1.14-3.06)	0.013	2.08 (1.23-3.51)	0.006
Age difference	1.04 (0.76-1.54)	0.838	1.09 (0.76-1.57)	0.640	1.10 (0.75-1.92)	0.451	1.33 (0.81-2.19)	0.250

[a] per 2 SD increase in growth parameters: 4.3 kg/year for peak weight velocity; 16 cm/year for peak height velocity; 1.2 months for age at BMIP; 2.1 kg/m^2 for BMI at BMIP; 2.1 years for age at BMIR; 2.2 kg/m^2 for BMI at BMIR

Table 4. Serum concentrations of IGF-1 at birth, 9 months and 2 years.

	IGF-1 (ng/ml), Median (IQR)					
	N	At birth	N	9 months	N	2 years
Islet autoantibody status						
positive	29	82.6 (71.0-99.7)	46	35.0 (27.0-53.0)	15	48.4 (27.2-59.1)
negative	48	79.5 (62.6-101.6)	51	34.3 (25.0-54.0)	15	46.9 (31.6- 64.1)
Gender						
Male	34	77.0 (61.8-96.0)	54	32.3 (24.0-45.3)	16	47.0 (29.0-59.5)
Female	43	87.0 (69.0-103.0)	43	43.0 (28.5-59.6)	14	51.7 (31.6-62.2)
Maternal type 1 diabetes status						
Yes	23	79.0 (54.1-95.0)	32	39.5 (31.6-57.0)	16	49.1 (31.5-67.7)
No	54	82.5 (67.0-101.8)	65	32.4 (25.3-47.0)	14	47.5 (30.8-62.2)
Cesarean section						
Yes	20	74.1 (56.8-89.4)	35	37.0 (31.0-59.6)	9	47.0 (41.6-62.2)
No	55	86.0 (67.0-104.0)	60	33.6 (23.5-47.3)	21	48.4 (30.8-59.1)
Large for gestational age status (LGA)						
Yes	19	94.0 (82.6-101.9)	20	45.2 (30.2-60.0)	6	47.1 (34.9-54.8)
No	53	76.7 (61.1-99.7)	73	33.1 (26.0-49.0)	24	48.3 (31.1-63.2)

Table 5. Serum concentrations of IGFBP-3 at birth, 9 months and 2 years.

	IGFBP-3 (ng/ml), Median (IQR)					
	N	At birth	N	9 months	N	2 years
Islet autoantibody status						
positive	29	1684 (1525-1922)	46	2108 (1627-2725)	15	2702 (2365- 3111)
negative	48	1582 (1396-1812)	51	2220 (1801-2655)	15	2639 (1953-2774)
Gender						
Male	34	1566 (1425-1774)	54	1968 (1587- 2365)	16	2539 (1990-2713)
Female	43	1661 (1445-1905)	43	2448 (1824-2796)	14	2869 (2454-3111)
Maternal type 1 diabetes status						
Yes	23	1655 (1390-1922)	32	2352 (1854-2824)	16	2689 (2048-3177)
No	54	1627 (1443-1814)	65	2011 (1648-2537)	14	2671 (2365- 2774)
Cesarean section						
Yes	20	1517 (1318-1707)	35	2198 (1802-2464)	9	3097 (2774-3300)
No	55	1684 (1481-1922)	60	2079 (1632-2734)	21	2572 (2142-2724)
Large for gestational age status (LGA)						
Yes	19	1661 (1524-1922)	20	2514* (2168-2995)	6	2410 (2142-2639)
No	53	1631 (1409-1884)	73	2080* (1648-2476)	24	2713 (2209-2967)

* P-value of Mann-Whitney-Test <0.01

Figure Legend

Figure 1. Mean of body mass index (BMI) values with 95% confidence intervals over time connected via piecewise polynomial splines (BMIP: Infant BMI peak, BMIR: childhood BMI rebound) in boys and girls, respectively.