Growth differences between North American and European children at risk for type 1 diabetes

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Abstract

Aim—To evaluate the relationships between early growth and regional variations in type 1 diabetes (T1D) incidence in an international cohort of children with familial and genetic risk for T1D.

Methods—Anthropometric indices between birth to 5 years of age were compared amongst regions and T1D proband in 2160 children participating in the TRIGR study.

Results—Children in Northern Europe had the highest weight z-score between birth-12 months of age, while those in Southern Europe and the United States had the lowest weight and length/height z-scores at most time points (P<0.005-P<0.001). Few differences in z-score values for weight, height and BMI were found by maternal T1D status. Using International Obesity Task Force criteria, the obesity rates generally increased with age and at 5 years were highest in males in Northern Europe (6.0%) and in females in Canada (12.8%). However, no statistically significance difference was found by geographic region. In Canada, the obesity rate for female
children of mothers with and without T1D differed significantly at 4 and 5 years (6.0 vs. 0.0% and 21.3% vs. 1.9%, respectively; \( P < 0.0125 \)) but no differences by maternal T1D status were found in other regions.

**Conclusions**—There are regional differences in early childhood growth that are consistent with the higher incidence of T1D in Northern Europe and Canada as compared to Southern Europe. Our prospective study from birth will allow evaluation of relationships between growth and the emerging development of autoimmunity and progression to T1D by region in this at-risk population of children.

**Keywords**
Type 1 diabetes mellitus; growth; North America; Europe

**Introduction**

The incidence of type 1 diabetes (T1D) in young children is increasing worldwide and is predicted to continue to increase in future years (1). The cause of T1D is considered to be a combination of genetic predisposition and environmental or lifestyle risk factors. Environmental triggers believed to influence the expression of the disease include viruses such as Coxsackie B, early introduction of foreign proteins and growth parameters (2). Recent observations of global increases in birth weight as well as trends for greater weight, height and body mass have led to the hypothesis that accelerated pediatric growth may contribute to the increasing incidence of T1D in children (3). Two physiological mechanisms have been proposed to explain this association as well as a younger presentation of the disease. 1) beta-cell hypermetabolism with hyperinsulinemia can be induced by insulin resistance that is a consequence of excess weight and inadequate physical activity (4). These metabolically active beta cells may be vulnerable to autoimmune attack as *in vitro* data have shown such beta cells to be more susceptible to cytokine damage than beta cells at rest (5). 2) Insulin resistance with associated increased insulin demands may result in presentation of hyperglycemia with relative rather than absolute insulin deficiency earlier in the beta-cell destructive process (6). In the studies that have examined the relationship between anthropometric growth parameters and the incidence of childhood diabetes, significant positive associations have been found between birth weight, birth length and increased growth measures during infancy or early childhood and risk for T1D (7–13).

The causes of childhood obesity are multifactorial with predisposing genetic factors and environmental components that include socio-economic status, physical activity and nutrition (14). Maternal diabetes during pregnancy has been associated with an increased prevalence of childhood obesity (15). Fetal exposure to increased concentrations of glucose is hypothesized to stimulate fetal hyperinsulinism, increased fat deposition and macrosomia. A recent study that examined the effect of maternal T1D on childhood overweight in offspring found that those born large for gestational age were at increased risk of overweight at all ages while maternal T1D did not contribute further (16).

Across continents, incidence of T1D is lowest in Asia, followed by Southern/Central Europe, Australia, and the United States and highest in Northern Europe and Canada (17). In this report we compared growth parameters and rates of obesity by region over a 5-year period in a uniformly selected cohort of 2,160 participants in the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study who have a first-degree relative with T1D and carry HLA-conferred susceptibility to T1D. We hypothesized that early childhood anthropometric measures observed in each region and country cohort will parallel the incidence rates of T1D observed across the globe. Furthermore, to examine the effect of maternal T1D on
Methods

The TRIGR study is an international T1D prevention trial designed to determine whether weaning to a highly hydrolyzed infant formula reduces the incidence of T1D in children with a first-degree relative with T1D and increased HLA-defined genetic risk. The trial was approved by the Ethics Institutional Review Boards and Committees of Human Experimentation in all participating TRIGR center institutions. A full description of the TRIGR study design has been reported previously (18). Over two-thousand children (N=2,160) at increased risk for developing T1D from the United States, Canada, Australia and 12 countries in Europe were recruited for the trial between May 2002 and January 2007. Children are being monitored until 10 years of age for the frequency of T1D associated autoantibodies and/or the development of clinical diabetes. As part of the TRIGR study protocol, anthropometric indices were obtained at birth and at each study visit. Available data to date at 3, 6, 9, 12, 18, 24, 36, 48 and 60 months of age are included in this analysis.

We compared mean z-scores for length/height (cm), weight (kg), and BMI (kg/m2) between TRIGR participants in both arms of the study in Australia (AUS), Canada (CAN), Northern Europe (NEUR; Finland, Sweden), Southern Europe (SEUR; Italy, Spain), Central Europe I (CEURI; Czech Republic, Estonia, Hungary, Poland), Central Europe II (CEURII; Germany, Luxembourg, The Netherlands, Switzerland) and the United States (USA) using analysis of covariance to adjust for exclusive breastfeeding as well as regional differences in the proportion of offspring who had mothers with T1D. Rates of obesity were also compared by region after 24 months of age using logistic regression. We used the International Obesity Task Force (IOTF) BMI cut-off points for obesity by age and gender (19). The TRIGR cohort was also stratified according to the presence or absence of maternal T1D by region. One thousand and ninety-six (1,096) children had affected mothers (51%) with the following regional proportions: AUS 55%, CAN 56%, NEUR 37%, SEUR 61%, CEURI 60%, CEURII 48% and USA 51%. Growth parameters and rates of obesity were compared between children born to mothers with and without T1D in each region using the t-test and Chi-square statistics, respectively. The Bonferroni correction method was used to address the problem of multiple comparisons. Accordingly, a p value of <0.005 was considered statistically significant for the anthropometric analysis and a p value of <0.0125 was considered statistically significant for the rates of obesity comparisons.

Results

Mean z-score values for anthropometric measures are shown by region and gender in Figures 1–6. Significant differences in weight were observed between regions until 18 months of age (p<0.005 to p<0.001). Males in SEUR had the lowest weight at each time point and females in the USA had the lowest weight except at 6 months. The highest weight of all regions between birth and 12 months of age was seen in infants in NEUR, while children in CAN had the highest weight at 18 months. At 5 years, these trends persisted with the highest weights in NEUR in males and in CAN in females. For males, the greatest length was found in CEURII at birth. Thereafter, children in NEUR had the greatest length at most time points with significantly higher measures at 3, 6 and 18 months (p<0.005 to p<0.001). The lowest length was found in children in SEUR at birth and 6 months, at 9 and 12 months (females only) and at 18 months (males only). Significant differences in BMI z-score were found for males at 36 months with the highest value in AUS and lowest in CEURII (p<0.001) and for females at 24 and 36 months with the highest values in AUS and CAN and lowest values in the USA and CEURI, respectively (p<0.001). The overall proportion of
children who were obese did not differ significantly between regions at any time point (Table 1). However, at later time points the obesity rate at 60 months was highest in NEUR (6.0%) for males, while for females the rate was highest in CAN (12.8%). In summary, overall the babies in the more northern climates were heavier and taller and later were more likely to be obese, with some gender variations.

Few differences in z-score values for weight, height and BMI were found by maternal T1D status. We observed higher weight at birth in infants born to mothers with vs. without T1D in CEURI female infants only (0.55 vs. 0.01, respectively, p<0.005). By 3 months of age, offspring of mothers with T1D had a lower mean weight than children of unaffected mothers in NEUR (males 0.44 vs. 0.76, p<0.005; females, 0.30 vs. 0.81, p<0.001) and in CAN (males, 0.28 vs. 0.70, p<0.005), respectively. This difference continued in NEUR for males at 6 months (0.18 vs. 0.52, p<0.005). Early length differences between children born to mothers with vs. without T1D were also found, the former being shorter at 3 months in NEUR (males, 0.26 vs. 0.63; females, 0.25 vs. 0.69, p<0.001), CAN (males, −0.09 vs. 0.34, p<0.001). No differences were found in obesity rates in males by maternal T1D status (Figure 7). However, the frequency of obesity was higher in children of mothers with vs. without T1D at 48 and 60 months of age in females in CAN (6.0 vs. 0.0% and 21.3% vs. 1.9, respectively; p<0.0125) (Figure 8).

Discussion

Differences in early childhood growth measures in the TRIGR population were observed between countries in North America and Europe, some unanticipated. The higher early childhood weight and length measures are consistent with the higher incidence of T1D in NEUR and Canada compared to their Southern counterparts (17), which supports a relationship but does not determine causality. In contrast, obesity rates did not follow this geographic distribution. Thus, if there is a relationship between early growth parameters and the frequency of T1D, this suggests that growth acceleration rather than obesity may explain the association. However, given that our primary study outcome, diagnosis of type 1 diabetes, will not be known until the end of the trial in the year 2017, a direct evaluation of the association between growth patterns and risk of T1D in TRIGR cannot yet be made. In addition it has to be kept in mind that the TRIGR participants who progress to type 1 diabetes will represent familial diabetes accounting for about 10% of all children with newly diagnosed disease, whereas incidence rates are based on both sporadic and familial cases. On the other hand there are data indicating that there is a correlation between the proportion of familial cases and the disease incidence in the background population (20). The EURODIAB Substudy 2 Study Group (8), Hypponen et al. (21), and Blom et al. (22) found higher values for weight and height during early childhood prior to the diagnosis of T1D. Longitudinal assessment of growth and weight velocities are needed to explore this possibility further.

Surprisingly, only in CEUI was birth weight in children of mothers with T1D significantly higher than in children whose mothers did not have T1D. Studies in various regions of Europe and North America have retrospectively examined neonatal anthropometric measurements in populations of children that have been diagnosed with T1D. Dahlquist et al. (7) reported an association between higher birth weight and T1D while Podar et al. (9) found an association between higher birth length and T1D compared to the general population. Hummel et al. (16) observed that maternal T1D was not independently associated with risk of childhood overweight at 2 and 5 years of age but also noted that factors associated with maternal T1D, such as high birth size, predispose children to overweight during adulthood. We did not find significant differences in birth weight of children by maternal T1D status, which may be the result of successful diabetes prenatal
care. However, our data do show higher later rates of obesity in children born to mothers with T1D vs. children with a different affected first-degree relative in the TRIGR cohort with the highest prevalence in Canada.

BMI has become an accepted measuring tool to diagnose weight concerns such as underweight, overweight or obesity in individuals and populations. The IOTF has developed BMI cut-off points for overweight and obesity by age and gender which are considered to be less arbitrary and more internationally based than the BMI tables developed by the Centers for Disease Control and Prevention in the United States (23–24). Among obese children, BMI is a good indicator of excess body fat. However, elevated BMI levels in overweight children can be the result of increased levels of lean or fat mass (25). In addition, greater weight at birth likely represents greater lean rather than fat mass. Our secondary analysis study has some limitations. Body composition measures were not obtained. Therefore, we cannot make an accurate assumption about the distribution of lean body mass and adipose tissue in our population.

The international and contemporary composition of our study population is a considerable strength and allows for direct comparisons by age and gender. As is widely known, the prevalence of childhood obesity is increasing in most industrialized countries with rates tripling in the last several decades. In a 2006 report by Wang and Lobstein (24), the rate of obesity in school-age children was predicted to be 10% in Europe and 15.2% in the Americas by the year 2010. The accelerator hypothesis introduced by Wilkin in 2001 (3) proposes that the overload of the beta cells due to increased insulin demand may initiate autoimmunity and accelerate the process of beta-cell destruction and lead to earlier development of T1D. Wilkin et al. (2002) has also reported that birth weight has little impact on insulin resistance (IR) in contemporary children, whereas current weight and weight gained after birth correlated with IR at 5 years of age (26). The view from the Pittsburgh group is that obesity-related IR may result in earlier disease expression at a given level of autoimmune islet destruction (27). Surprisingly, there was a lack of statistical significance by geographic region. However, obesity rates in the TRIGR population generally increased with age. The size of the cohort will allow an assessment of the role of obesity in further increasing the risk of later development of T1D in a population already genetically predisposed.

In summary, the prospectively collected data of this large study will allow assessment of the still controversial hypothesis that either accelerated growth parameters and/or obesity are associated with the worldwide increase in the incidence of T1D. Although ecologic trends are similar for the increases of both, there is dissociation between the prevalence of childhood obesity and the lower T1D risk with maternal T1D (28–29). The causes of elevated birth weight and childhood obesity are a combination of genetic factors and intrauterine as well as postnatal metabolic and environmental influences. Prevention strategies aimed at reducing the risk of overweight and obesity in children, such as promoting breastfeeding, reducing energy intake, maintaining energy balance and increasing physical activity, continue to be logical, if only to reduce the risk of co-morbid conditions such as insulin resistance and heart disease. Our prospective study from birth will allow evaluation of relationships between growth and the emerging development of autoimmunity and progression to T1D by region in this at-risk population of children.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.
Acknowledgments

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References

25. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institutes of Health. Body Mass Index: Considerations for Practitioners. Atlanta, GA:
Figure 1.
Weight z-scores by region (males)
m = months
AUS – Australia, CAN – Canada, NEUR – Northern Europe, SEUR – Southern Europe,
CEURI – Central Europe I, CEURII – Central Europe II, USA – United States
* $P<0.005$, † $P<0.001$
Figure 2.
Weight z-scores by region (females)

m = months
AUS – Australia, CAN – Canada, NEUR – Northern Europe, SEUR – Southern Europe,
CEUR I – Central Europe I, CEUR II – Central Europe II, USA – United States

*P<0.005, †P<0.001
Figure 3.
Height z-scores by region (males)
m = months
AUS – Australia, CAN – Canada, NEUR – Northern Europe, SEUR – Southern Europe,
CEURI – Central Europe I, CEURII – Central Europe II, USA – United States
*P<0.005, †P<0.001
Figure 4.
Height z-scores by region (females)
m = months
AUS – Australia, CAN – Canada, NEUR – Northern Europe, SEUR – Southern Europe,
CEURI – Central Europe I, CEURII – Central Europe II, USA – United States
* $P<0.005$, † $P<0.001$
Figure 5.
Mean body mass index by region (males)
m = months
AUS – Australia, CAN – Canada, NEUR – Northern Europe, SEUR – Southern Europe,
CEURI – Central Europe I, CEURII – Central Europe II, USA – United States
†P<0.001
Figure 6.
Mean body mass index by region (females)
m = months
AUS – Australia, CAN – Canada, NEUR – Northern Europe, SEUR – Southern Europe,
CEURI – Central Europe I, CEURII – Central Europe II, USA – United States
†P<0.001
Figure 7.
Percent of male TRIGR participants who are obese using International Obesity Task Force (IOTF) criteria by region and maternal type 1 diabetes status
AUS – Australia, CAN – Canada, NEUR – Northern Europe, SEUR – Southern Europe,
CEURI – Central Europe I, CEURII – Central Europe II, USA – United States
Figure 8.
Percent of female TRIGR participants who are obese using International Obesity Task Force (IOTF) criteria by region and maternal type 1 diabetes status
*p<0.0125 (comparison of values by maternal type 1 diabetes status)
AUS – Australia, CAN – Canada, NEUR – Northern Europe, SEUR – Southern Europe, CEURI – Central Europe I, CEURII – Central Europe II, USA – United States
Table 1

Percent of TRIGR participants who are obese using International Obesity Task Force (IOTF) criteria by region and gender

<table>
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<tr>
<th></th>
<th>AUS</th>
<th>CAN</th>
<th>NEUR</th>
<th>SEUR</th>
<th>CEURI</th>
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<td>24 m</td>
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<tr>
<td>M</td>
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<td>1.3 (241)</td>
<td>0.4 (252)</td>
<td>0.0 (42)</td>
<td>3.5 (144)</td>
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<td>2.4 (205)</td>
<td>1.0 (199)</td>
<td>2.1 (47)</td>
<td>1.8 (112)</td>
<td>0.0 (77)</td>
<td>2.0 (150)</td>
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<tr>
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<td>2.3 (132)</td>
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<td>2.6 (77)</td>
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<td>M</td>
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<td>2.8 (181)</td>
<td>3.1 (191)</td>
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<td>2.5 (80)</td>
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<td>9.2 (65)</td>
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The values are indicated as % (n)

AUS – Australia, CAN – Canada, NEUR – Northern Europe, SEUR – Southern Europe, CEURI – Central Europe I, CEURII – Central Europe II, USA – United States