Infant Feeding, Early Weight Gain, and Risk of Type 1 Diabetes

ELINA HYPPÖNEN, MSC, MPH
MIKE G. KENWARD, PHD
SUVI M. VIRTANEN, MD, DMSC, MSC
ARI PIITULAINEN, MB
PAULA VIRTA-AUTIO, MSC
JAAKKO TUOMILEHTO, MD, DMSC
MIKAEL KNIP, MD, DMSC
HANS K. ÅKERBLOM, MD, DMSC
THE CHILDHOOD DIABETES IN FINLAND (DIME) STUDY GROUP

OBJECTIVE — To evaluate whether the increased risk of type 1 diabetes conferred by an early introduction of cow's milk supplements can be mediated by accelerated growth in formula-fed infants.

RESEARCH DESIGN AND METHODS — All children ≤14 years of age who were diagnosed with type 1 diabetes from September 1986 to April 1989 were invited to participate in the study. Birth date– and sex-matched control children were randomly selected from the Finnish Population Registry. At least three weight measurements from the first year of life were obtained for 435 full-term diabetic subjects and 386 control subjects from well-baby clinics and school health care units.

RESULTS — Increase in body weight was greater in the diabetic girls than in the control girls, and the difference increased from 111 g (95% CI 0–218, $P = 0.04$) at 1 month of age to 286 g (95% CI 123–450, $P = 0.0006$) at 7 months. For boys, the difference in weight between the diabetic subjects and the control subjects remained stable during infancy (difference 95 g, 95% CI −2–205, $P = 0.09$). Increased weight was associated on average with a 1.5-fold risk of type 1 diabetes. Early introduction of formula feeding (<3 vs. ≥3 months) was also associated with an increased risk of type 1 diabetes after adjustment for the individual weight gain curve (adjusted odds ratio 1.53, 95% CI 1.1–2.2). No evidence for interaction was observed.

CONCLUSIONS — These observations indicate that an early exposure to cow's milk formula-feeding and rapid growth in infancy are independent risk factors of childhood type 1 diabetes.

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There is evidence indicating that accelerated prenatal growth (1) and increased weight gain in infancy may act as risk factors for childhood type 1 diabetes (2,3). In several case-control studies, early introduction of cow's milk formula-feeding has been associated with an increased risk of type 1 diabetes, although contradictory findings have been published as well (4,5). It is well-known that breast-fed healthy infants tend to grow more slowly than formula-fed infants (6,7). Among the present series, it has previously been shown that the introduction of supplementary milk-feeding at an early age increases the risk of type 1 diabetes, regardless of the total duration of breast-feeding (8). Therefore, it was interesting to explore whether the effect of increased risk of childhood type 1 diabetes, which again is caused by an early introduction of cow's milk formula-feeding, could be mediated via the effects of feeding on growth.

From the School of Public Health (E.H., S.M.V., P.V.-A.), Medical School (M.K., A.P.), and Tampere Diabetes Research Center (E.H., S.M.V., P. V.-A., M.K.), University of Tampere; the Department of Pediatrics (S.M.V., M.K.), University Hospital, Tampere, Finland; the Department of Epidemiology and Public Health (M.G.K.), London School of Hygiene and Tropical Medicine, London; the National Public Health Institute (J.T.), Helsinki; and the Hospital for Children and Adolescents (H.K.Å.), University of Helsinki, Helsinki, Finland.

Address correspondence and reprint requests to Elina Hyppönen, School of Public Health, University of Tampere, P.O. Box 607, FIN-33101 Tampere, Finland. E-mail: elina.hypponen@uta.fi.

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Abbreviations: BF, breast-fed; FF, formula-fed; OR, odds ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

— All Finnish children ≤14 years of age who were diagnosed with type 1 diabetes between September 1986 and April 1989 were invited to participate in the nation-wide case-control study, "Childhood Diabetes in Finland" (9). Data on infant feeding practices were made available for 750 of the 801 (94%) children who were diagnosed during the recruitment period. The random population-based control children, who were birth date– and sex-matched, were selected from the Finnish Population Registry. After three attempts, 690 (85%) of the diabetic subjects were matched with control subjects. Copies of growth charts and records for 586 diabetic subjects and 571 control subjects were obtained from well-baby clinics and school health care units.

The analyses in this article require not only a degree of consistency to describe the pattern of growth, but also sufficient information to describe this pattern for each individual. Children born prematurely display quite different patterns of growth than those born full-term. For these reasons, children born at least 2 weeks before their dates of expectancy (12% of the diabetic subjects and 13% of the control subjects) and those with less than three available weight measurements over the first year of life have been excluded, thereby leaving data for 435 diabetic subjects and 386 control subjects for the present analysis. The number of weight observations from 2 weeks to 1 year of age was 3,523 for the diabetic subjects and 3,299 for the control subjects. The mean number of individual measurements was 8.1 (median 8, range 3–15) for the diabetic subjects and 8.5 (median 8, range 3–21) for the control subjects.

Of both the diabetic and control children, 53% were boys. The mean age at diagnosis was 8.2 years (SD 3.6). Sociodemographic and dietary data were collected by means of structured questionnaires (available from the authors). Dietary data used in this study consisted of total duration of breast-feeding, and age at introduction of supplementary milk-feeding and solid foods. Reliable data concerning the type of infant formula (e.g., whey/casein predominant) was not available. The sociodemo-

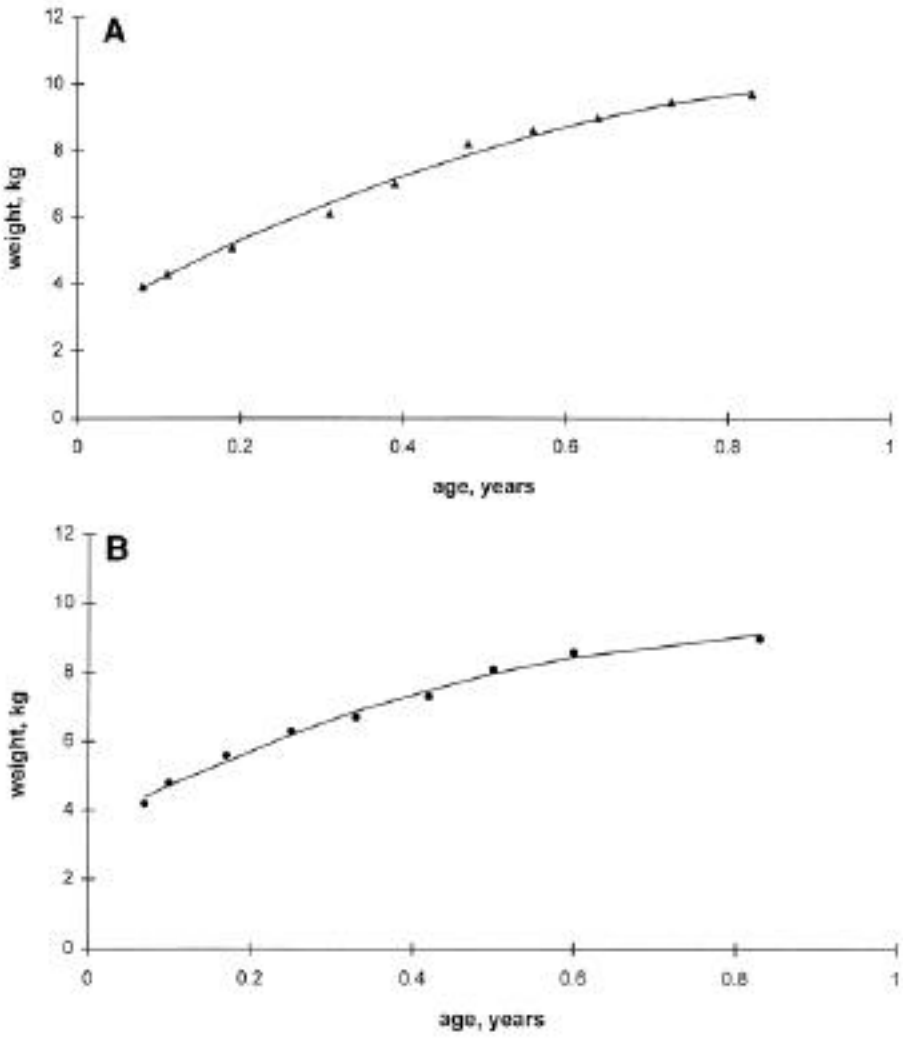

Figure 1—*Fitted individual curves with the absolute measurements for a randomly selected control child* (A) *and diabetic child* (B).

graphic variables used in this study were the length of maternal education (<10 vs. 10–12 vs. ≥13 years) and place of residence (urban vs. rural). Neonatal variables used in this study were the age of the mother at the time of childbirth (<30 vs. ≥30 years), and birth order (first born vs. others). There were no differences between the diabetic subjects and the control subjects in any of the sociodemographic or neonatal variables used. The study protocol was approved by the ethics committees of all the participating hospitals. Informed consent was obtained from the parents.

Data analysis

Two types of statistical analysis have been used. First, random coefficient models (10) have been applied to model the longitudinal weight measurements. In these models, each individual is assumed to follow his or her own growth trajectory, represented by a quadratic or cubic curve. The fitted individual curves with the original weight measurements for one randomly selected control subject and diabetic subject are presented in Fig. 1. The shape and intercept of the mean profiles were allowed to differ according to diabetic/control status and values of the other covariates as listed in the previous section. These models have been fitted using SAS PROC MIXED (SAS/STAT Software; SAS Institute, Cary, NC) (11). To avoid the distorting effects of immediate postnatal weight loss, measurements from the first 2 weeks have been excluded. In the component of the model that represents average weight, the pattern of development was allowed to change when at least 1 month had transpired since the introduction of infant formula or solid foods.

The second type of analysis used logistic regression to estimate the risk of developing type 1 diabetes in terms of infant feeding, early growth, and other covariates. These models were fitted using SPSS (SPSS, Chicago) (12). Individual growth summaries used as input in these models were provided by the fitted parameters of individual growth curves taken from a random coefficient model as described above. For this purpose, the random coefficient model included no covariates.

RESULTS — The proportion of children who received formula-feeding by the age of 3 months was 33% in the diabetic subjects and 25% in the control subjects ($P = 0.04$). Neither the total duration of breast-feeding nor the age at introduction of solid foods differed between the diabetic subjects and control subjects. Weight at birth did not differ significantly between the diabetic subjects and control subjects (for boys, 3,759 vs. 3,682 g, $P = 0.07$; for girls, 3,600 vs. 3,544 g, $P = 0.31$).

Girls weighed less than boys throughout the first year of life. The difference between the diabetic boys and the control boys remained stable to the age of 1 year (difference 95 g, 95% CI −2–205, $P = 0.09$). The diabetic girls grew faster than the control girls, and the difference increased from 111 g (95% CI 0–218, $P = 0.04$) at 1 month of age to 286 g (95% CI 123–450, $P = 0.0006$) at 7 months, after which the difference decreased to 204 g (95% CI −1–416, $P = 0.06$) on average at 11 months. The effect of formula-feeding on growth was found to be the same in the diabetic and control children (Fig. 2). Boys who had been given formula-feeding (FF) at least 1 month before the weight measurement weighed on average 42 g (95% CI 5–79, $P = 0.02$) more than breast-fed (BF) children of the same age (Fig. 2). Among girls, the FF children were consistently heavier than the BF children from 4 months of age (difference at 4 months 72 g, 95% CI 28–116, $P = 0.001$). Adjusting for the beginning of formula-feeding did not have an effect on the difference in weight between the diabetic and control children. Likewise, such factors as adjustment for age at the introduction of solid foods, total duration of breast-feeding, maternal education, maternal age, place of

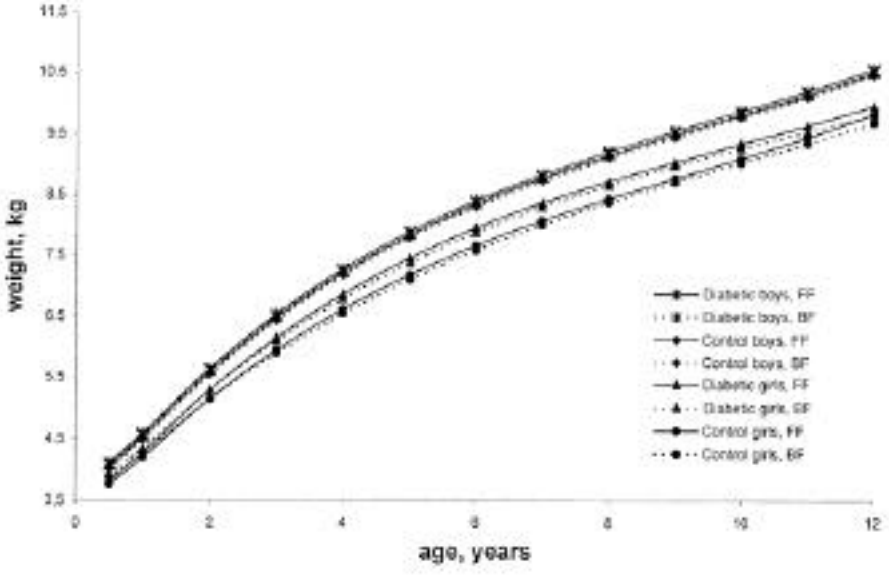

Figure 2—*Fitted mean weight increment by infant feeding.*

residence, birth order, birth weight, and target height did not affect the difference between the diabetic subjects and the control subjects.

Greater weight was associated with an increased risk of type 1 diabetes throughout infancy (Fig. 3), and there was no evidence of a difference in risk between boys and girls. Early age at the introduction of formula-feeding (<3 vs. ≥3 months) was associated with an increased risk of type 1 diabetes (odds ratio [OR] 1.57, 95% CI 1.1–2.2), and adjustment for the individual weight gain curve had no effect on this association (adjusted OR 1.53, 95% CI 1.1–2.2). The association between increased weight and risk of type 1 diabetes also remained after adjustment for early introduction of formula-feeding, and no interaction could be observed between these two risk factors in relation to the risk of type 1 diabetes (Table 1). The estimated height or ponderal index (weight/height^3) at 3, 6, 9, or 12 months of age was not associated with the risk of developing type 1 diabetes, independently of weight (data not shown).

CONCLUSIONS — It has been suggested that the association between early introduction of cow's milk formula-feeding and the risk of type 1 diabetes observed in the present series (8,13), as well as in several others (4), is mediated by increased growth induced by formula-feeding (3). In the present study, both early age at the introduction of cow's milk formula-feeding and an increased weight gain during infancy were associated with an increased risk of type 1 diabetes, and no evidence of interaction was observed. Adjustments for the total duration of breast-feeding, the introduction of solid foods in the child's diet, and target height, birth weight, and several sociodemographic variables did not affect the conclusions.

In the present study population, weight during infancy was the strongest anthropometric determinant associated with the risk of developing type 1 diabetes. Ponderal index is thought to reflect the soft tissue growth, whereas body weight is the combination of soft tissue growth and the length gain. Therefore, our results suggest that the weight gain during infancy in children who later develop type 1 diabetes is not abnormal, although it is greater than weight gain in the control children.

Evidence from an animal experiment indicates that weight gain in BB rats destined to develop autoimmune diabetes is increased from the first days of life (14). In humans, children who subsequently develop type 1 diabetes have been reported to weigh more than control children at certain time points in infancy. Baum et al. (2) reported that boys with type 1 diabetes were heavier than control boys at 6 months of age; the same was observed in girls at 12 months. In a Swedish series, a significant difference was observed in weight gain in both sexes from birth to 6 and 9 months between children who developed type 1 diabetes and control children (3). In girls, a significant difference in weight gain was also noted from birth to 18 and 30 months (3). In the present study in which weight development during the first year of life was evaluated, an enhanced weight gain could be observed in the diabetic girls compared with the control girls, and a small persistent difference between the diabetic boys and the control boys up to the age of 1 year. Moreover, we observed that the diabetic subjects and the control subjects who had received formula during the preceding 1-month period were on average heavier than breast-fed children of the same age; however, this weight increment induced by formula-feeding did not explain the differences in weight gain between the diabetic and the control children.

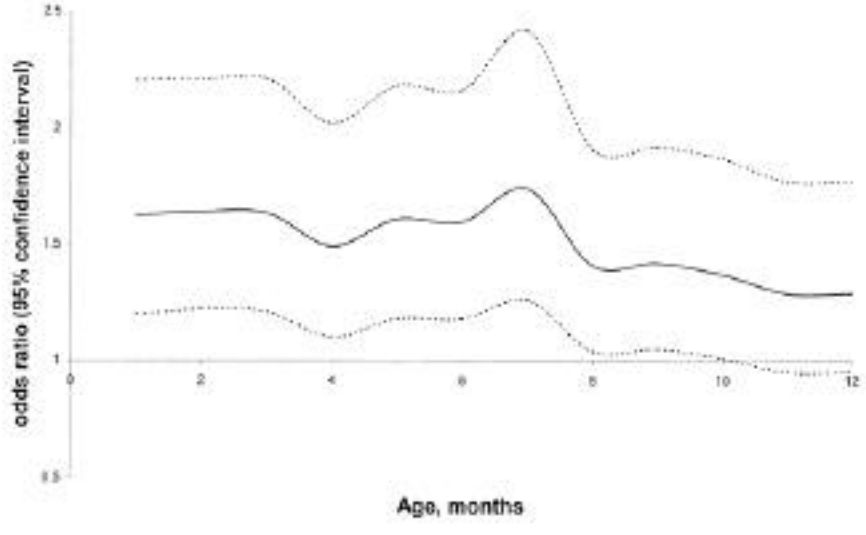

Figure 3—*Risk of type 1 diabetes by increased weight (highest quartile vs. others) in infancy.* **—**, *OR;* **- - -**, *CIs for the OR.*

Table 1—*Effect of early introduction of cow's milk formula feeding (<3 months vs. ≥3 months), increased weight (highest quartile vs. others), and their interaction on the risk of type 1 diabetes*

	Model 1*	Model 2†	Model 3‡
3 Months of age			
Formula	1.56 (1.1–2.2)	1.56 (1.1–2.2)	1.47 (1.0–2.2)
Weight	1.49 (1.1–2.1)	1.48 (1.1–2.1)	1.39 (0.9–2.1)
Formula*weight	—	—	1.23 (0.6–2.6)
−2 log. likelihood		952.967	952.653
6 Months of age			
Formula	1.56 (1.1–2.2)	1.53 (1.1–2.2)	1.47 (1.0–2.2)
Weight	1.42 (1.0–2.0)	1.39 (1.0–1.9)	1.33 (0.9–2.0)
Formula*weight	—	—	1.13 (0.6–2.3)
−2 log. likelihood		954.675	954.556
9 Months of age			
Formula	1.57 (1.1–2.2)	1.53 (1.1–2.2)	1.40 (0.9–2.1)
Weight	1.30 (0.9–1.8)	1.25 (0.9–1.7)	1.14 (0.8–1.7)
Formula*weight	—	—	1.31 (0.6–2.7)
−2 log. likelihood		956.765	956.185

Data are ORs (95% CI). The number of observations has been held constant in all models. *Formula and weight in separate models; †formula and weight adjusted for each other; ‡formula and weight with the interaction term.

Despite criticisms of the approach (15), repeated measurement analyses, such as growth comparisons, are still commonly made by using a series of comparisons of means at different times. In the present setting, to accommodate properly the longitudinal nature of these data, a random coefficient regression model has been used as a basis for assessing the differences in weight gain between the diabetic and control children. By using the longitudinal data modelling, we were also able to consider the changes in infant feeding patterns when assessing the differences in weight gain between the diabetic and control children.

Several mechanisms have been implied in mediating the diabetogenic effect of cow's milk, including the hypothesis on molecular mimicry between bovine serum albumin and the islet p69 protein, the casein fragment hypothesis, dysregulation of oral tolerance, and the recent idea that early exposure to bovine insulin could break the immune tolerance to human insulin (5). One possible common mechanism for the effect of both early introduction of formula-feeding and increased weight gain in infancy on the risk of type 1 diabetes could be hyperinsulinemia because hyperfunctioning β-cells have been observed to be more susceptible to cytotoxic effects of various cytokines (16). Infants have been found to elicit a smaller insulin response to feeding with human milk compared with cow's milk (17,18), and an increased insulin secretion induced by amino acids has been suggested to be a factor promoting growth in infants with high protein intakes (19). However, in the present study, formula-feeding and increased growth were associated with the risk of type 1 diabetes, irrespective of each other; and no evidence for interaction could be observed, indicating that neither of these two risk factors can be considered solely as a marker for the other.

According to present knowledge, type 1 diabetes is a multifactorial autoimmune disease where environmental factors alone, or more likely in different combinations, lead to the destruction of insulin-secreting β-cells and eventually to the onset of clinical disease in genetically susceptible individuals. The present findings support the view that both the introduction of cow's milk formula-feeding at an early age and increased weight gain in infancy are involved in the pathogenic process leading to the clinical onset of type 1 diabetes. In light of the present results, it seems likely that even if an early introduction of formula-feeding may result in overfeeding and thus increase β-cell stress, increased growth alone cannot explain the association between the early introduction of cow's milk and an increased risk of type 1 diabetes.

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APPENDIX

Members of the DiMe Study Group

Principal Investigators, H.K. Åkerblom and J. Tuomilehto; Coordinators, R. Lounamaa and L. Toivanen; Data Management, J. Pitkäniemi and E. Virtala; Local Investigators, A. Fagerlund, M. Flittner, B. Gustafsson, C. Häggqvist, A. Hakulinen, L. Herva, P. Hiltunen, T. Huhtamäki, N.-P. Huttunen, T. Huupponen, M. Hyttinen, T. Joki, R. Jokisalo, M.-L. Käär, S. Kallio, E.A. Kaprio, U. Kaski, M. Knip, L. Laine, J. Lappalainen, J. Mäenpää, A.-L. Mäkelä, K. Niemi, A. Niiranen, P. Ojajärvi, T. Otonkoski, K. Pihlajamäki, S. Pöntynen, J. Rajantie, J. Sankala, J. Schumacher, M. Sillanpää, M.-R. Ståhlberg, C.-H. Stråhlmann, T. Uotila, M. Väre, P. Varimo, and C. Wetterstrand; and Special Investigators, A. Aro, M. Hiltunen, H. Hurme, H. Hyöty, J. Ilonen, J. Karjalainen, M. Knip, P. Leinikki, A. Miettinen, T. Petäys, L. Räsänen, H. Reijonen, A. Reunanen, T. Saukkonen, E.Savilahti, E. Tuomilehto-Wolf, P. Vähäsalo, and S.M. Virtanen.

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