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Growth and Nutrition in the Etiology of Type 1 Diabetes



ACADEMIC DISSERTATION

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List of original publications

The study consists of the following publications referred to in the text with the roman numerals (I–IV). In addition, some previously unpublished data are presented.

- I Hyppönen E, Kenward MG, Virtanen SM, Piitulainen A, Virta-Autio P, Tuomilehto J, Knip M, Åkerblom HK, and the Childhood Diabetes in Finland Study Group (1999): Infant feeding, early weight gain and risk of Type 1 diabetes. *Diabetes Care* 22: 1961–1965.
- II Hyppönen E, Virtanen SM, Kenward MG, Knip M, Åkerblom HK, and the Childhood Diabetes in Finland Study Group (2000): Obesity, increased linear growth and risk of insulin-dependent diabetes mellitus. *Diabetes Care* 23: 1755–1760.
- III Virtanen SM, Hyppönen E, Läärä E, Vähäsalo P, Kulmala P, Savola K, Räsänen L, Aro A, Knip M, Åkerblom HK, and the Childhood Diabetes in Finland Study Group (1998): Cow's milk consumption, disease associated autoantibodies and IDDM: A follow-up study of siblings of children with diabetes. *Diab Med* 15: 730–738.
- IV Hyppönen E, Läärä E, Reunanen A, Järvelin MR, and Virtanen SM. Are low intake of vitamin D and suspicion of rickets associated with the risk of Type 1 diabetes? – Evidence from a birth-cohort study in northern Finland. *Lancet*, in press.

Abbreviations

BB rat	bio-breeding rat
BMI	body mass index
cDNA	complement strand DNA
CI	confidence interval
DiMe	Childhood Diabetes in Finland
GAD	glutamic acid decarboxylase
GH	growth hormone
HLA	human leucocyte antigen
HR	hazard ratio
IAA	insulin autoantibody
IA-2A	antibodies to the insulinoma associated cDNA2 protein
ICA	islet cell autoantibody
ICP model	infancy-childhood-puberty model
IGF	insulin like growth factor
IU	international unit
NOD mouse	non-obese diabetic mouse
OR	odds ratio
SDS	standard deviation score

1 Introduction

Type 1 diabetes is an autoimmune disease resulting from progressive destruction of insulin secreting beta-cells (Atkinson and Maclaren 1994, Bach 1994). Over the past 20 years, investigation of the etiology of type 1 diabetes has been very active, but the exact pathogenic destruction process or factors affecting it remain only partly understood. However, it is generally accepted that genetic predisposition as well as exposure to environmental agents are required for the development of type 1 diabetes. There are also indications that the process leading to the destruction of the beta-cells may be very lengthy, and that the effect of an early environment may be of crucial importance (Lindberg et al. 1999).

Incidence of type 1 diabetes in Finland is higher than anywhere else in the world (Karvonen et al. 2000). Since the first nation-wide survey in the early 1950s (Somersalo 1955) an over four-fold increase in the incidence of type 1 diabetes has been observed among Finnish children and adolescents, and a marked increase has also been observed in many other industrialized countries (Onkamo et al. 1999). The reasons for this worrying trend remain unknown, although it is evident that such a steep increase cannot solely result from enrichment of susceptibility genes for type 1 diabetes. Changes in the human environment have been manifold since the Second World War, and especially in industrialized countries great improvements in the general hygienic and nutritional status of the populations have occurred. A secular increase in growth has been observed and also the prevalence of obesity has been increasing during the past decades. In addition, changes have occurred in food processing as well as in the dietary recommendations made for the general public.

The purpose of the present study was to evaluate whether growth or nutrition in infancy or later in childhood are associated with the risk of type 1 diabetes. As child growth is known to be very strongly affected by diet, the joint effect of early growth and selected factors in the infant diet were also investigated in relation to the risk of type 1 diabetes.

2 Literature review

2.1 Growth in infancy and childhood

Growth of an individual is the phenotypic expression of interaction of both genetic and environmental factors, and it represents a long process starting from conception (Tanner 1992, Hauspie and Susanne 1998). In humans, the term growth generally refers to changes in the size and shape of the body.

A secular increase in the attained body size has occurred in almost all industrialized countries during the past century (Hauspie et al. 1997). Also, the prevalence of childhood obesity has been increasing during the past decades (Porkka et al. 1997, Chinn and Rona 2001). The secular trend in growth, may be considered as an indicator of the changes in the (early) nutritional, hygienic, and health status in the populations (Tanner 1992). However, it has also been suggested that secular growth is due to greater mobility of individuals during the past decades resulting in more genetically heterogeneous and thus more vigorous offspring (van Wieringen 1986).

According to the infancy-childhood-puberty (ICP) model of growth (Karlberg et al. 1987a,1987b) the biology of growth is divided into three distinct periods: infancy, childhood, and puberty. The infancy period lasts up to the first three years of life and represents a period of very fast but rapidly decelerating growth. The childhood component of growth starts already around the age of six months, and until the age of two to three years is a combination of infancy and childhood components. The third, pubertal, period of growth describes the adolescent growth spurt stimulated by sex steroids. According to the ICP growth model, the normal shape of a growth curve results from the additive effects of first the infant, secondly the childhood, and finally the pubertal components of growth. Although on the whole the process of growth may be seen to be linear, it consists of periods of slow growth as well as of spurts of very fast height/weight increment when divided into shorter intervals (Wales 1998). After birth, growth rate is greatest in infancy. The rate of growth decreases gradually from infancy until adulthood, with growth spurts in mid-childhood (6 to 8 years) and puberty (Bogin 1998). Seasonal variation in the rate of growth has been described, and fastest growth reported during the periods of maximum sunlight availability (Bogin 1998).

2.1.1 Genetic influences on growth

Normal growth is strongly genetically determined (see Hauspie and Susanne 1998). It is thought that the heritability of growth is polygenic and has influences both on growth tempo and potential. It is further believed that genetic factors may modify the effect of environment on growth. Children normally tend to grow along a genetically determined growth trajectory. Even if the growth of a child is disturbed by some adverse condition, children often return to their own growth trajectory by a period of accelerated so called catch-up growth if the growth-disturbing conditions are removed (Golden 1998).

Most evidence for the genetics of growth is derived from comparisons between twins, family studies or population comparisons (Hauspie and Susanne 1998). The concordance in height has been reported to be markedly stronger between monozygotic than dizygotic twins (Wilson 1979). In comparisons between parents and offspring, the correlation coefficients have usually been found to be around 0.4–0.5 (Kuh and Wadsworth 1989, Alberman et al. 1991). Adjustment for indicators of social conditions have been observed to have a negligible effect on the association between heights of parents and their offspring (Rona and Chinn 1995). Although family studies also suggest genetic component to childhood obesity, such studies are not usually able to separate genetic factors from influences of shared environment (Towne 1998). However, according to a Swedish study on identical twins that were reared apart, the intra-pair correlation coefficient for body mass index (BMI) was as high as 0.7 and did not differ significantly from that for twins reared together (Stunkard et al. 1990).

It has long been known, that additional Y chromosomes, and also to some extent additional X chromosomes result in taller individuals, while the lack of sex chromosomes leads to stunting (Hauspie and Susanne 1998). During the past decade progress has been made in identifying single genes determining growth, such as genes coding for GH (e.g. GH1 and GH2 genes, chorionic somatomammotropin gene) (see Miyata and Phillips 1998). The insulin gene region, which is a known susceptibility locus for type 1 diabetes, has been found to be associated with size at birth (Dunger et al. 1998). In addition, a gene encoding IGF-II has been identified near the insulin gene region (Paquette et al. 1998). It has also been proposed that the vitamin D receptor gene contributes to early postnatal growth (Keen et al. 1997, Suarez et al. 1997).

2.1.2 Environmental influences on growth

Variation in individual heights may largely be explained by differences in their genotypes, however, at least in an ethnically homogenous setting variation in mean height between groups of individuals is largely determined by environmental factors (Tanner 1992).

Adequate nutrition, both in terms of nutrients and energy is fundamental for normal growth; early growth in particular is largely nutritionally determined. Obesity, which generally results from excessive energy intake in relation to energy expenditure, leads to faster height gain (Vignolo et al. 1988). On the other hand, linear growth may be impaired even when energy and protein intake are adequate, indicating the importance of other dietary factors (Allen 1994). Attempts to reverse growth stunting by interventions with single vitamins or micro-nutrients (e.g. vitamin A, zinc, copper, iodine) have given inconsistent results, and a beneficial effect has typically been observed only in the presence of a deficiency of the nutrient in question (Allen 1994, Rosado 1999). It has been suggested that in most cases growth retardation is associated with marginal deficiencies of several micro-nutrients (Rosado 1999).

Weight gain is known to be greater in formula fed infants compared to breast fed children (Salmenperä et al. 1985, Dewey et al. 1995). The decrease in the energy content in breast milk from initiation of lactation until weaning is likely to contribute to this difference. Also the increase in the lipid content of human milk from the beginning of the feed until the end, is likely to contribute to the regulation of the appetite of the child. Infants have also been found to elicit a smaller insulin response to feeding with human milk compared to cow's milk (Ginsburg et al. 1984, Salmenperä et al. 1988). Increased insulin secretion induced by amino acids has been suggested to be a factor promoting growth in infants with high protein intakes (Axelsson et al. 1989).

The effects of vitamin D on growth are well established. In children, a severe deficiency of vitamin D (i.e. rickets) leads to growth retardation and deformation of the skeleton. Cholecalciferol, the active form of vitamin D, is known to increase the absorption of calcium from the intestine and control the rate of skeletal remodeling and mineralisation of new bone tissue (Fraser 1995).

There is an association between childhood infections and growth faltering (Stephensen 1999). This association is most likely explained by nutrition, as infections may decrease food intake, impair nutrient absorption (e.g. due to diarrhoea), as well as increase the metabolic requirements or catabolic losses of nutrients (Allen 1994, Stephensen 1999).

Social class differences in growth are well documented (Tanner 1992, Baxter-Jones et al. 1999). The secular increment in attained height as well as in tempo of growth has been observed to be more pronounced in children from low socio-economic backgrounds, or of poorly educated parents compared to others (Hauspie et al. 1997). Although the social differences in growth have diminished during the past decades, they are still believed to be present in most populations. Relative weight shows a less regular pattern with social indicators than does height, although in industrialized countries there is a tendency for lower social classes to have a greater weight for height and a higher prevalence of obesity compared to higher classes (Bielicki 1986). In the Northern-Finland Cohort 1966 Study, a better social status was found to be positively associated with the mean BMI at birth, but inversely at 1 and 31 years of age (Laitinen et al. 2001). Findings from a British cohort study found the social class differences in overweight and obesity to be negligible during childhood, where as an association with early social conditions was observed in young adulthood (Power and Moynihan 1988).

2.1.3 Hormonal regulation of growth

Growth hormone (GH) is known to be responsible for normal growth during childhood (see Hindmarsh 1998), but the age at which GH begins to control growth is uncertain (Karlberg 1998). Linear fetal growth is almost independent of GH, and even during the first 6 months of life, growth has been observed to be close to normal in GH deficient children. During infancy growth is believed to consist of both nutritionally driven fetal growth and GH dependent childhood growth. Prenatal growth is mainly influenced by insulin and insulin like growth factors (IGFs) (Hernandez 1998).

The excretion of growth hormone is regulated by two hypothalamic peptides, i.e. growth-hormone releasing hormone and somatostatin (Hindmarsh 1998). Receptors for GH are found in most cells of the body, and GH is able to initiate a wide range of functions including fat metabolism, long-bone and soft tissue growth, as well as insulin action. The effect of GH is mediated by an increase in the production of IGF-I e.g. in the growth plates of the bone. IGF-I is bound to binding proteins in the circulation. Although the principal regulators of IGF-I are GH and nutrition, its bioactivity is largely determined by binding proteins. In addition to GH, thyroid hormones, sex steroids and insulin are needed for normal growth in childhood. Relatively little is known about the relationships between the variation in the output of particular hormones and the variation in the pattern of growth in healthy individuals (Johnston 1998).

2.2 Epidemiology and pathogenesis of type 1 diabetes

Incidence rates of type 1 diabetes vary over 350 fold globally (Karvonen et al. 2000) and there is wide variation even inside relatively genetically homogenous areas such as Europe (EURODIAB ACE Study Group 2000). Incidence of type 1 diabetes in Finland is the highest in the world, and in 1998 a record high overall rate of 50 cases per 100,000 years at risk was observed for children under 15 years old (Reunanen A, personal communication). This is more than four times higher than that reported in the first Finnish nation-wide survey in 1953 (12 per 100,000 years at risk, Somersalo 1955). A steep increase in the incidence of type 1 diabetes during the past decades has been observed both in countries of high and low incidence (Onkamo et al. 1999), some studies indicating that the increase has been the greatest for children younger than 5 years of age (Karvonen et al. 1999).

A global north-south gradient in the incidence of type 1 diabetes was debated in the 1980s (Rewers et al. 1988). Later studies on the trends of incidence of type 1 diabetes globally as well as inside Europe have failed to show any persistent patterns, and geographical variation seems to reflect mainly the global distribution of the major ethnic groups stressing the importance of genetic factors (Karvonen et al. 2000). However, as the genetic code in humans changes very slowly, it is not possible to explain the very steep increase in the incidence of type 1 diabetes without considering the effect of changes in the human environment.

2.2.1 Autoimmune process

Type 1 diabetes is an autoimmune disease and among the most common chronic disorders in children and young adults (see Atkinson and Maclaren 1994, see Bach 1994). Although the exact pathological pathways leading to the development of type 1 diabetes remain unknown, it is generally believed that this process is affected by environmental agents operating within a genetically susceptible individual. The process leading to the destruction of insulin secreting beta-cells and thus to the development of the disease may be long and initiated several years before the actual diagnosis of the condition, possibly even before birth (Lindberg et al. 1999). According to histological studies, clinical diabetes emerges when approximately 80% of the beta-cells have been destroyed (Gepts 1984).

Chronic inflammatory infiltrate (i.e. insulinitis) consisting of CD8 and CD4 T-cells, B lymphocytes, macrophages and natural killer cells is found in the islets of Langerhans near the time of onset of type 1 diabetes, as well as in patients with long-standing

disease (Foulis et al. 1991). Evidence from the two main animal models of type 1 diabetes, namely non-obese diabetic (NOD) mouse and bio-breeding (BB) rat, suggest that T-cells have a key role in infiltrating the islets in the pancreas and in destroying the insulin producing beta-cells (Bach 1994). Although T-cells are thought to have an important role in the autoimmune process, peripheral T-cells have so far failed to qualify as a surrogate marker for the development of the disease (Schloot et al. 1999). As the pancreas is not accessible for investigation in humans, the immunologic effector mechanisms must be studied using the peripheral blood cells, which may not fully correspond to the immunological mechanisms occurring within the pancreas (Atkinson and Maclaren 1994).

More than 25 years ago, autoantibodies to islet cells (ICA) were found among patients with newly diagnosed diabetes (Botazzo et al. 1974, MacCuish et al. 1974). Although the methodology for detection, as well as the classification of diabetes associated autoantibodies has changed since, the occurrence of autoantibodies in the peripheral blood are the best known markers of type 1 diabetes in humans to date. Autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD) and to the insulinoma associated cDNA2 protein (IA-2A) have been observed years before the manifestation of hyperglycaemia, indicating a very long disease process (Kulmala et al. 1998). However, even a broad humoral autoimmune response (as exhibited by presence of several diabetes associated autoantibodies) in a genetically susceptible individual, may not necessarily lead to the onset of the disease (Kulmala et al. 2000). A number of islet cell antigens have been associated with type 1 diabetes (see Atkinson and Maclaren 1994). It is possible that these antigens are directly involved in the pathogenic process leading to the development of type 1 diabetes, or they may merely represent targets of autoantibodies without independent pathological significance.

2.2.2 Genetic susceptibility

The effect of genetic factors on the occurrence of type 1 diabetes is undisputed. Studies show consistently higher concordance rates of type 1 diabetes for monozygotic than for dizygotic twins (Lo et al. 1991, Kaprio et al. 1992, Kyvik et al. 1995). However, as the concordance rate of type 1 diabetes even in monozygotic twins is estimated to be only 20 to 50%, it seems evident that genetic factors alone are not sufficient to cause the disease. In the Childhood Diabetes in Finland Study, the prevalence of type 1 diabetes among siblings of children with type 1 diabetes was about 3% at the time of diagnosis of the index child (Tuomilehto et al. 1992), increasing to approximately 5% after a 3-year follow up (Kaprio et al. 1992). Prevalence of type 1 diabetes in the dizygotic twins

of subjects with type 1 diabetes, has been found to be slightly higher (Kyvik et al. 1995) or to correspond to that of other siblings (Kaprio et al. 1992). Familial type 1 diabetes has also been observed to be associated with a younger age at onset of the disease (EURODIAB ACE Study Group and EURODIAB ACE Substudy 2 Study Group 1998). It should be noted, however, that only 10 to 15% of all new cases of type 1 diabetes, have a family history of the disease (Wagener et al 1982, Dahlquist et al. 1985, Tuomilehto et al. 1992).

Type 1 diabetes, which was still called ‘the genetics nightmare’ a few years ago, is believed to be a polygenic disease. The greatest disease susceptibility has been associated with human leukocyte antigen (HLA) genes (i.e. IDDM1 gene) on chromosome 6p21 (see Atkinson and Maclaren 1994, see Kida 1999). The association between HLA antigens and type 1 diabetes was first described in the early 1970s (Nerup et al. 1974). HLA molecules are involved in the immune-system recognition. HLA Class II molecules (in particular HLA-DQ and -DR) show the strongest association with type 1 diabetes, but these DNA specificities differ in different populations. In the Finnish population, the susceptibility to type 1 diabetes is strongly associated with DQB1 *0302 allele, and weakly with *0201 (Reijonen et al. 1991, Ilonen et al. 1996). Strong protection from type 1 diabetes has been associated with DQB1 *0602 and weak protection with *0301 allele. The effect of DQ locus may, however, be modulated by alleles in the DR locus (Nejetsev et al. 1999).

The insulin gene region (i.e. IDDM2 gene) on chromosome 11p15.5 has been identified as the other major site for susceptibility to type 1 diabetes (Kida 1999). The alleles in the insulin gene locus are classified according to the variable number of tandem repeats. Class I alleles have been positively associated with type 1 diabetes, while class III alleles have mainly been found to be protective (Bennett et al. 1995). The effect on the risk of type 1 diabetes by these alleles has been suggested to result from a more efficient deletion of autoreactive T-cells of Class III alleles compared to Class I alleles (Pugliese et al. 1997).

These two most important susceptibility genes for type 1 diabetes have been estimated to account for approximately 50% of its familiar clustering (Davies et al. 1994). Genome-wide scans have identified a number of additional susceptibility loci for type 1 diabetes, although their relative importance is thought to be less than those of the genes in the HLA or insulin region (Davies et al. 1994, Mein et al. 1998). Interestingly, recent observations from Europe (Pani et al. 2000) as well as from Asia (Chang et al. 2000, McDermott et al. 1997) indicate that vitamin D receptor gene polymorphisms may be associated with type 1 diabetes.

2.2.3 Environmental triggers, precipitators, and accelerators

Evidence that environmental factors must have a role in the pathogenic events leading to the development of type 1 diabetes comes from the steeply increasing incidence of type 1 diabetes (Onkamo et al. 1999), studies carried out among migrant populations (Elliot et al. 1989, Bodansky et al. 1992), and the low concordance rate observed in monozygotic twins (Kaprio et al. 1992). However, no single important component has so far been identified as the main pathogenic agent for type 1 diabetes. It seems likely that the effect of environmental factors may differ according to life stage. They may act at different stages of the pathogenic process, multiple hits may be needed, and interactions between different environmental exposures as well as with genetic factors further complicate the issue (Åkerblom et al. 1997).

Some dietary factors (e.g. cow's milk, nitrites/N-nitroso compounds) as well as viral infections (e.g. enteroviruses) are proposed to be possible independent initiators for the autoimmune process leading to the destruction of beta-cells (Dahlquist 1998). The effect of an environmental factor in the initiation of the autoimmune process may occur at different stages (Greenbaum et al. 1994). It is possible that the environmental agent affects the beta-cell antigen directly, the presentation process of the beta-cell antigen, or the regulation of T – and B-cell function. On the other hand, factors increasing the need for insulin or the systemic levels of cytokines may accelerate the ongoing beta-cell destruction (Nerup et al. 1988, see Rossini et al. 1993). Further, exposures increasing the peripheral need for insulin are associated with the disease onset as they unmask the insulin deficiency, rendering the disease overt (Dahlquist 1998). It has been suggested that e.g. increased growth rate, infections, and stress could act as environmental accelerators or precipitators for the process of ongoing beta-cell destruction (Dahlquist 1998). In the following, studies on growth preceding the diagnosis of type 1 diabetes, as well as on the effect of selected dietary factors on the risk of type 1 diabetes are reviewed in more detail.

Growth and the development of type 1 diabetes

Current understanding of the association between growth and the development of type 1 diabetes is relatively poor, and does not allow a clear cut positioning of growth in the scaling of “gene-environment” or on “marker-risk factor” axes. In this literature review growth is mainly treated as a reflection of nutritional status i.e. an indicator of environmental exposure potentially affecting the risk of type 1 diabetes. This could be true, as hyperfunctioning beta-cells have been shown to be more susceptible to the cytotoxic

effect of various cytokines (Nerup et al. 1988), and a greater energy intake increasing the secretion of insulin is reflected in an increased growth and/or obesity.

Infancy Baum and co-workers (1975) were the first to report a difference in absolute weight in infancy between children who subsequently develop type 1 diabetes and control children. They reported a greater weight in boys who later developed type 1 diabetes at 6 months of age compared to children remaining free of diabetes, and the same was observed in girls at 12 months. In a later Swedish study, a significant difference in weight gain was observed between children who developed type 1 diabetes and controls (Johansson et al. 1994). In both sexes the difference was observed from birth to 6 and 9 months, and in girls additionally from birth to 18 and 30 months. A more recent study comparing the development of relative weight [presented as body mass index (BMI)], found a tendency to overweight, but no difference in length, during the first year of life in children who subsequently developed type 1 diabetes compared to non-diabetic siblings (Bruining 2000). In a nested case-control study children who had converted to positive for at least one diabetes associated autoantibody by 4 years of age were observed to be similar than other children in their relative weight and length at 12 months of age (Kimpimäki et al. 2001).

Childhood Greater height, but not greater weight, at time of diagnosis have been reported in several case-control studies comparing children with newly diagnosed type 1 diabetes with non-diabetic controls (see Drayer 1974). However, many of these early reports used the existing growth standards as the reference population, indicating a possible effect of secular changes of growth to these differences. On the other hand, weight loss before the disease onset is a well known symptom of type 1 diabetes. Also, a tendency to decreased growth velocity has been observed during the final year preceding diagnosis (Leslie et al. 1991, Price and Burden 1992).

More evidence for a differing pattern of height growth in children who subsequently develop type 1 diabetes, comes from two case-control studies published in 1992. In these studies children with type 1 diabetes and control children were compared on the basis of information obtained from their growth charts. An English study reported that children who later developed type 1 diabetes were already 3 years before the diagnosis taller than their controls (Price and Burden 1992). In a Swedish series, prediabetic boys were reported to be taller than controls even 7 years prior to diagnosis (Blom et al. 1992). No significant difference in height was observed between case and control girls, although the estimates in their study were in the same direction for both sexes. In a more recent, although relatively small study, no difference in length/ height

was observed between children who developed type 1 diabetes and their siblings, under the age of 5 years (Bruining 2000).

Even less is known about the pattern of growth in weight before the diagnosis of type 1 diabetes. Bruining (2000) did not find any significant differences in relative weight, indexed by BMI between 1 and 5 years of age when comparing children who developed type 1 diabetes to their siblings. Further, Blom and colleagues (1992) reported similar weight for height in case and control children. However, in the Swedish study 45 percent of the case children were diagnosed at 10 years of age or older (Blom et al. 1989). As the authors state, they were able to define relative weight for a maximum height of 146 cm for boys and 137 cm for girls (Blom et al. 1992). In the risk assessment they used the relative weight between 5 and 1 years before the diagnosis so it seems possible that obese children may have been selectively excluded from the risk assessment, given that obese children are characterized by increased height velocity (Vignolo et al. 1988).

Parental height There are few comparisons between the heights of the parents of children with type 1 diabetes and the parents of unaffected children, and most studies have observed no differences (Drayer 1974, Songer et al. 1986, Bruining 2000). One relatively recent study reported that mothers of children with type 1 diabetes were taller than growth reference data (Scheffer-Marinus et al. 1999). Information on the tempo of growth for the parents was not available in any of the studies.

One study has observed relative height at the time of diagnosis of type 1 diabetes to be greater than the relative target height determined on the basis of heights of the parents in children who were between 5 and 9 years of age at diagnosis (Brown et al. 1994). However, relative height at any time during childhood depends on age as well as on the tempo of growth. Any comparison between the parental height and the attained final height by the child with type 1 diabetes, is complicated by the issue of growth being dependent on the glycemic control of the disease (Wise et al. 1992).

Dietary factors in the development of type 1 diabetes

The first suggestion of the effect of diet on the development of type 1 diabetes in man, came from an ecological observation from Iceland published in the early 1980s (Helgason and Jonason 1981). A greater prevalence of type 1 diabetes was observed in boys born in October compared to others. The authors suggested that this could be associated with the traditional consumption of smoked/cured mutton by the parents around Christmas-time. Icelandic smoked/cured mutton, was rich in diabetogenic N-

nitroso compounds, and it was suggested that the diabetogenicity could be transferred to the male offspring through paternal germ cells (Helgason and Jonason 1981, Helgason et al. 1982). Streptozotocin, a compound belonging to N-nitroso compound family, is known to be directly toxic to beta-cells, and has been extensively used in inducing type 1 diabetes in experimental animals (Lampeter et al. 1989, Buschard 1991).

In subsequent animal experiments, ecological comparisons, and observational studies in humans, more evidence for the diabetogenic effect of N-nitroso compounds has been obtained. However, also a large number of other dietary factors have been associated with the risk of type 1 diabetes (see Åkerblom and Knip 1998). The effect of age at introduction of cow's milk supplements on the risk of type 1 diabetes, is the factor most extensively studied and debated. In addition several other foods and food constituents (e.g. gluten/wheat products, coffee, soy), have been suggested to increase the risk of type 1 diabetes (Åkerblom and Knip 1998). Protective effect from type 1 diabetes has been suggested for breast feeding (Borch-Johnsen et al. 1984, Mayer et al. 1988), dietary antioxidants (Glatthaar et al. 1988, Knekt et al. 1999), as well as for vitamin D (EURODIAB Substudy 2 Study Group 1999, Stene et al. 2000). Placebo controlled trials aiming at the prevention of type 1 diabetes by supplementation with nicotinamide have been undertaken among autoantibody positive first degree relatives of patients with type 1 diabetes. However, in the first published report of a randomized double-blind trial, no beneficial effect of nicotinamide was observed and the first phase insulin release was even decreased in subjects receiving the treatment (Lampeter et al. 1998). Enough evidence has not been gathered yet to draw final conclusions about the effect of any nutritional factor in the development of type 1 diabetes.

Infant feeding and cow's milk consumption In many studies the duration of breast feeding has been observed to be shorter in children who later developed type 1 diabetes (Borch-Johnsen et al. 1984, see Åkerblom and Knip 1998). After initial observations of an inverse association between the risk of type 1 diabetes and duration of breast feeding, it was suggested that breast milk may protect from the development of diabetes by protecting the infant from viral infections (Borch-Johnsen et al. 1984). However, later observations from the Childhood Diabetes in Finland (DiMe) Study, indicated that breast feeding had no independent association with the risk of type 1 diabetes, when the age at introduction of cow's milk supplements was taken into account (Virtanen et al. 1993).

Cow's milk proteins have been observed in some, albeit not all, animal experiments to be diabetogenic in BB rats and NOD mice (Elliot and Martin 1984, see Åkerblom and Knip 1998). Also in several case-control studies an association between

the age at introduction of cow's milk formula feeding and the risk of type 1 diabetes has been observed. According to two meta-analyses published on the subject, the risk of type 1 diabetes was increased by approximately 40% in children who had been formula fed before the age of 3 months (Gerstein 1994, Norris and Scott 1996). So far, follow-up studies have been relatively modest in size and able to investigate the effect of breast feeding or early introduction of cow's milk formula only in relation to the occurrence of diabetes associated autoantibodies. An Australian study sample (Couper et al. 1999), comprised of 22 children who had seroconverted to positive for two autoantibodies, and 70 children that were positive for one autoantibody. In the German BABYDIAB Study (Hummel et al. 2000), during the 2 years of follow-up 31 children seroconverted to positive and 10 children developed diabetes. Neither of the studies found a significant association between any infant feeding variable investigated and the development of beta-cell autoimmunity. A recent observation from a Finnish nested case-control study indicated a markedly increased risk of seroconversion to positive for IA-2A autoantibodies by 4 years of age if the child had received cow's milk before the age of 2 months compared to those receiving it at the age of 4 months or older (Kimpimäki et al. 2001). Also the risk for seroconversion to positive to all the four investigated autoantibodies (namely ICA, IAA, IA-2A, and GADA) was increased. However, no significant association of infant feeding indicators with any other combination of multiple autoantibodies was found.

Results are conflicting in the few studies investigating the effect of milk consumption later in childhood on the risk of type 1 diabetes. In a Swedish series, cow's milk consumption was lower in newly diagnosed cases of type 1 diabetes compared to controls (Dahlquist et al. 1990), whereas cow's milk protein intake in an Australian study was observed to be greater in the cases of type 1 diabetes than in control children (Verge et al. 1994). In the DiMe Case-Control Study no association between cow's milk consumption and type 1 diabetes was observed (Virtanen et al. 1994). However, after adjustment for genetic markers of type 1 diabetes an increased risk of type 1 diabetes was observed for those children consuming at least 3 glasses of milk daily compared to others (OR 1.5, 95% CI 1.0–2.2) (Saukkonen et al. 1998). In this study siblings of the case children were used as the referent group because information on genetic factors was not available from the control children.

Immune responses to cow's milk proteins have been observed to be elevated in children with newly diagnosed type 1 diabetes in several studies (Savilahti et al. 1988, Vaarala et al. 1996, see Åkerblom and Knip 1998). Levels of antibodies to cow's milk proteins have been observed to be associated both with infant feeding (Dahlquist et al. 1992, Virtanen et al. 1994) as well as with childhood milk consumption (Virtanen et al. 1994).

Cow's milk could increase the risk of type 1 diabetes by several mechanisms. Cow's milk formula has been observed to contain bovine insulin, which could break the self-tolerance to human insulin through an immunization process in the infant (Vaarala et al. 1998). Alternatively, early introduction to cow's milk formula feeding may be diabetogenic due to immune system defects in the gut, reflecting disturbed oral tolerance to cow's milk (Vaarala et al. 1996). According to the so called molecular mimicry theory, immunization to bovine serum albumin present in cow's milk could lead to the destruction of the beta-cells due to an observed homology between bovine serum albumin and a structural protein in the membrane of the beta-cell (Martin et al. 1991). The association between early introduction to formula feeding and subsequent risk of type 1 diabetes has also been suggested to be mediated via the effects of feeding on growth (Johansson et al. 1994), as formula fed children are known to grow faster than breast fed ones (Dewey et al. 1995). Among other theories, it has also been suggested that the diabetogenicity of cow's milk is related to the beta casein fractions in the cow's milk (Elliott et al. 1997). The issue of the association between exposure to cow's milk and the risk of type 1 diabetes, as well as the underlying mechanisms remain debated.

Vitamin D In studies carried out in experimental animals, supplementation with vitamin D has been observed to protect from insulinitis (Mathieu et al. 1992) as well as from the development of type 1 diabetes (Mathieu et al. 1994, Casteels et al. 1998). In humans, to date there are only two case-control studies investigating the association between vitamin D supplementation and subsequent risk of type 1 diabetes. In a Norwegian study, maternal cod liver oil supplementation during pregnancy was associated with a reduced risk of type 1 diabetes in the off-spring (Stene et al. 2000). Vitamin D intake of the mother is known to be reflected in the vitamin D status of the new-born infant (Delvin et al. 1986, Zeghoudd et al. 1997). There was some evidence of a protective effect of cod liver oil administered during the first year of life from the development of type 1 diabetes, but no evidence for an association between the intake of vitamin D supplementation and the risk of type 1 diabetes (Stene et al. 2000). However, vitamin D supplements usually contain much smaller amounts of vitamin D than is obtained from the use of cod liver oil. In an earlier multi-center case-control study, vitamin D supplementation in infancy was associated with on average a 33% reduction in the risk of type 1 diabetes (EURODIAB Substudy 2 Study Group 1999). As vitamin D is obtained mainly through production in the skin induced by exposure to ultraviolet radiation, also an ecological observation of correlation between mean daily sunlight hours and the incidence of type 1 diabetes has been proposed as evidence

suggesting an association between vitamin D and type 1 diabetes (Dahlquist and Mustonen 1994).

Immunosuppressive effects of vitamin D are well established, and in addition to type 1 diabetes it has been observed to protect from other autoimmune diseases (e.g. arthritis, and thyroiditis, Bikle 1992). The most likely explanation of the effect of vitamin D on the development of type 1 diabetes would seem to be through immunomodulation, as it is generally accepted that cytokines, T-cells and macrophages all have a role in the autoimmune process leading to the destruction of beta-cells and thus to the development of type 1 diabetes (Bach 1994). It may also be possible that vitamin D metabolism is associated with the genetic susceptibility to type 1 diabetes. In some studies polymorphism's of vitamin D receptor gene have been associated with the risk of type 1 diabetes (McDermott et al. 1997, Chang et al. 2000, Pani et al. 2000), although contradictory findings have also been reported (Klupa et al. 1999).

3 Objectives

The aims of the present study were :

1. To investigate the effect of growth during infancy (I) and later in childhood (II) on the risk of type 1 diabetes.
2. To investigate the effect of nutrition in infancy (III, IV) and later in childhood (III) on the risk of type 1 diabetes.
3. To evaluate the joint effect of growth and nutrition in infancy on the risk of type 1 diabetes (II, IV).

4 Subjects and methods

4.1 Childhood Diabetes in Finland (DiMe) Study

All hospitals in Finland treating children with diabetes took part in the recruitment phase of the Childhood Diabetes in Finland (DiMe) Study (Tuomilehto et al. 1992). This prospective population based family survey was designed to investigate genetic, environmental and immunological influences on type 1 diabetes. A schematic illustration of the aspects of the DiMe Study relevant to current thesis is presented in Figure 1.

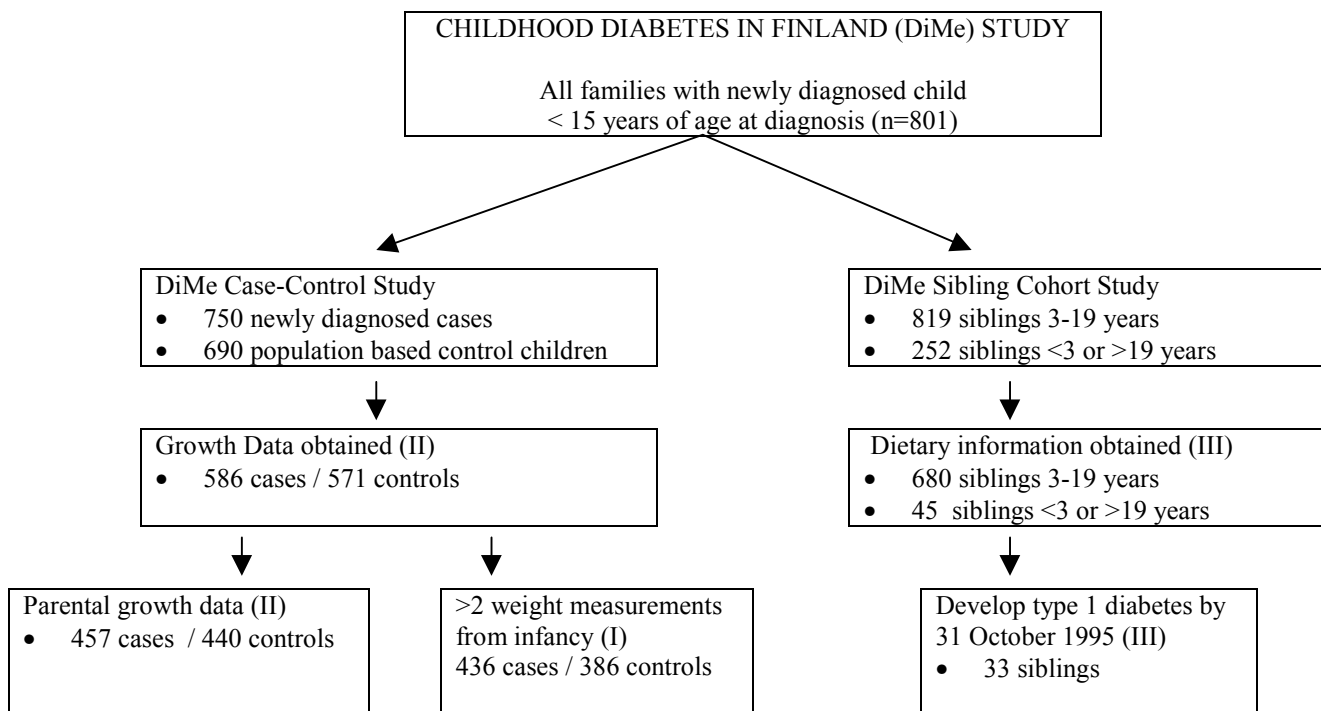


Figure 1. Schematic presentation of the Childhood Diabetes in Finland (DiMe) Study.

4.1.1 DiMe Case-Control Study (I, II)

Subjects

Between September 1986 and April 1989 all children with newly diagnosed type 1 diabetes <15 years of age were invited to participate in the DiMe Case-Control Study (I, II, Figure 1). Blood samples from the index children were analyzed for type 1 diabetes associated autoantibodies (ICA, IAA, GADA, and IA-2A), and 98% of the cases were found to be positive for at least one of the four antibodies (Savola et al. 1998), confirming the presence of autoimmune, i.e. type 1 diabetes. Of the total of 801 affected children invited, 94% took part in the study. One control child was selected for each case from three potential sex matched control subjects. Controls were randomly selected from the Finnish Population Register: one born the same day, one born the day before and one born the day after. Of the control children first selected (i.e. born the same day) 62% participated and after three attempts, 85% of the case children had controls. Controls for the early onset type 1 diabetes cases (age at diagnosis <7 years) were prospectively selected from the Finnish Population Register from May 1988 to April 1989. Control children for the remainder of the cases, were chosen after the completion of the study (November 1989 to August 1990).

For the analyses investigating the effect of childhood growth on subsequent risk of type 1 diabetes (II) the sample consisted of all the case and control children for whom growth data was obtained (586 cases and 571 controls, Figure 1). Data on parental height was available for 457 cases and 440 controls. For the evaluation of the joint effect of infant feeding and weight gain on the risk of type 1 diabetes (I), the sample was restricted to the full-term cases and controls with information on at least three weight measurements during the first year of life (435 cases and 386 controls).

Data collection and measures of exposure

Information on dietary, neonatal, and socio-demographic characteristics was obtained by means of structured questionnaires from the cases after the diagnosis of type 1 diabetes. The questionnaires were mainly filled in by the mothers. For the control children (n=112) matched with the early onset cases with diabetes (< 7 years), the questionnaires were completed during an interview at a home visit. The parents of the remainder of the controls received and returned the study questionnaires by post.

The dietary questionnaire included questions on the total and exclusive duration of breast-feeding, age at the introduction of cow's milk supplements and solid foods. An exact length of gestation was not known, but a birth was defined as premature, if it had been reported by the mother to have occurred at least 2 weeks before the expected date of delivery. The length of maternal education was classified as low or intermediate (< 13 years), or high (\geq 13 years). Place of residence of the child was divided in to urban or rural (outside community centers).

Growth data (parental heights and child's height, weight and measurement dates) and copies of growth charts were requested by letter from the nurses at the child welfare centres and school health care units. If the nurse responsible for child's health did not answer within 1 month, one reminder letter was sent. For most children the information was obtained as numerical data, but for 12% of the cases and 9% of the controls all the measurements were read from the growth curves. A summary of growth measurements available in the analyses for the Studies I and II are presented in Table 1.

Table 1. Number of available weight(I) and paired weight/height (II) measurements by age in the Childhood Diabetes in Finland Case-Control Study.

	Cases		Controls	
	All n (%)	Individual median (range)	All n (%)	Individual median (range)
Study I				
<1 year	3,523	8 (3–15)	3,299	8 (3–21)
Study II				
0–1.9 years	5,505 (66)	9 (1–19)	5,139 (49)	9 (1–25)
2–9.9 years	2,578 (31)	5 (1–13)	4,060 (39)	7 (1–15)
\geq 10 years	261 (3)	2 (1–9)	1,280 (12)	3 (1–11)

4.1.2 DiMe Sibling Cohort Study (III)

Subjects

All the unaffected 3 to 19 year-old siblings (n=819) of the index children of the DiMe Case-Control Study were invited to the DiMe Sibling Cohort Study (III, Figure 1). Information on diet was available for 82% (n=725) of the siblings. In addition, the study population included siblings under 3 (n=37) and over 19 (n=8) years of age. Study participation among the sibling cohort was as follows; only one sibling participated in the study from 324 families, two from 138 families, three from 25 families, four from six families, and six from three families. From one family there were eight participating siblings.

Data collection and measures of exposure

After the diagnosis of type 1 diabetes in the index child, information on potential risk factors for diabetes was collected from their siblings using similar questionnaires to those used for the index cases (4.1.1). The questions on childhood diet for the siblings focused on the half year period before entering the study. Information on usual combined daily milk and sour milk consumption (in glasses, 1 glass 180 ml), and consumption frequencies of milk, sour milk, yogurt, ice cream, and cheese were used in evaluating the effect of childhood milk product consumption on the subsequent risk of type 1 diabetes (III).

Outcome and follow-up measures

Presentation with clinical type 1 diabetes over the time period from the diagnosis of diabetes in the index child until October 31, 1995 was used as the main outcome measure. Information on the newly diagnosed cases of type 1 diabetes was obtained from the Central Drug Register of the Finnish Social Insurance Institution using record linkage (Reunanen et al. 1982). Insulin medication for diabetes in Finland is free of charge for all patients, and all the subjects receiving this benefit are registered at the Central Drug Register.

4.1.3 Ethical considerations

The ethical committees of all the participating hospitals had approved the study protocol. Informed consent was obtained from the participating families.

4.2 Northern-Finland Cohort 1966 Study (IV)

4.2.1 Subjects

The Northern-Finland Cohort 1966 study is a population-based prospective birth cohort study in the two northernmost provinces of Finland (Oulu and Lapland) (Rantakallio 1969). All the pregnant women with an expected date of delivery in 1966, and whose pregnancies continued after the 24th week of gestation (n=12,068) as well as their new-

born children were eligible for the original study. The women were recruited at their routine visit to municipal maternity health centre during the 7th or 8th month of pregnancy. All maternity health centers in the area participated in the study, and the vast majority of the deliveries took place at the hospitals in the area. The study cohort consists of a total of 12,321 deliveries, representing 96% of all deliveries that occurred in the area during the target period. A small number of births occurred towards the end of 1965 and early 1967. The original title of the study was “North Finland Premature Birth Study” and the initial purpose was to describe risk factors for prenatal deaths and low birth weight. Out of all deliveries 173 were still births and 280 deaths occurred in the first year of life. Of those children alive at 1 year of age, 91% participated in the 1-year-follow-up survey (n=10,821) (Rantakallio and Mäkinen 1983). After restriction to those subjects with data on the use of vitamin D supplementation in infancy in total 10,366 records were available for the investigation of association between vitamin D and subsequent risk of type 1 diabetes (IV).

4.2.2 Data collection and measures of exposure

Information on prenatal and social factors was collected at recruitment by a structured questionnaire (Rantakallio 1969). An effort was made to obtain the information in the 24th to 28th week of gestation, but 10% of women completed the questionnaire later in pregnancy or after delivery. The classification of the social class at the time of birth was based on the prestige of father’s occupation if the mother was married, and that of the mother if single, widow, or divorced (Alestalo and Uusitalo 1978, Olsen et al. 1995). The social class was divided in the following categories: 1) professionals and other white collar workers, 2) skilled workers, 3) unskilled workers, and 4) farmers. Marital status was divided into 1) married and 2) unmarried; and maternal education into 1) basic or less (i.e. under 9 years compulsory elementary school) and 2) intermediate or more.

A questionnaire about the delivery and the new-born infant was filled in by the midwives in the maternity hospitals (Rantakallio 1969). Data on the length of gestation, birth weight and length were collected from obstetric records. The assessment of gestational age was based on the traditional calculation from the date of last menstrual period.

In 1967 a questionnaire was sent to the child welfare centres, and the public health nurses were asked to make a special examination of the child at the age of 1 year (Rantakallio and Mäkinen 1983). The questionnaires were complemented with information from the child’s health charts, and supplemented with information obtained during the

examination performed by public health nurses and general practitioners. There were on average 10 contacts with a child welfare centre during the first year. For 95% of the cases the information was collected when the child was at least 11.5 months of age (Ranta-kallio et al. 1985). The frequency of vitamin D supplementation during the first year of life was provided by the mother, and classified as 1) regular, 2) irregular, and 3) none. The dose of vitamin D received daily was calculated on the basis of the concentration of vitamin D in the product used and the reported amount of the product consumed. For the purposes of the analyses the dose was divided into 1) recommended ($\geq 2,000$ IU/day), and 2) below recommendation ($< 2,000$ IU/day) (Hallman et al. 1964). Information about suspected rickets during the first year of life, was collected using a question defining rickets as “suspected by the health care personnel”. A combined variable indicating overall adequacy of vitamin D intake was constructed. Inadequacy was determined either on the basis of intake of vitamin D supplementation (receiving none, or low dose of vitamin D) or by suspicion of rickets.

4.2.3 Outcome and follow-up measures

Diagnosis with type 1 diabetes by the end of 31st December 1997 was used as the main outcome measure. Cases with type 1 diabetes were identified from the Central Drug Register of the Finnish Social Insurance Institution via record linkage using the personal identification number as previously described (Reunanen et al. 1982). Type of diabetes was ascertained from the hospital discharge registers, and/or from the medical files for all the cases aged 20 years or more at the time of diagnosis. The follow-up for each individual lasted up to diagnosis with diabetes (n=81), date of emigration (n=565), death (n=215), or the end of the study. The exact dates of death were obtained by record linkage from the National Register of Causes of Death, maintained by Statistics Finland. For those subjects living abroad who participated in the follow-up survey in 1997 the year of emigration was obtained from a questionnaire filled in by the participants. For the remainder, the date was obtained by the reported date of the emigration of the mother by 1997 when available, or by estimating the date to be the mid point between the last contact with the subject and the end of follow-up.

4.2.4 Ethical considerations

The Ethics Committee of the Faculty of Medicine of University of Oulu keeps the collection and use of the material of the Northern-Finland Cohort 1966 Study under review. Permission to gather outcome data was obtained from the Ministry of Social Welfare and Health in 1993. In the field survey conducted in 1997, after complete description of the study, the subjects had an opportunity to deny the use of their data. A total of 83 individuals did not consent to the use of their data and were excluded.

4.3 Statistical analyses

4.3.1 Standardization of growth measures (II, IV)

For the analyses in Study II, relative weight was calculated as weight in relation to the mean weight for height and sex (100%), and relative height as a deviation of height in standard deviation scores (SDS) from the mean height for age and sex. The relative weight, the relative height and the target height were computed using software containing Finnish growth standards (Sorva et al. 1984, 1990 a, b, Pere 2000). None of the children in the present series exceeded the height limits for determination of relative weight (180 cm for boys, and 170 cm for girls). The parent-specific target height (Sorva et al. 1989) was corrected for secular growth as previously described (Pere et al. 1995).

Standardized birth weight and standardized growth rate (IV) were determined as the deviation in SDS from the sex specific mean birth weight/growth rate for corresponding age. In order to avoid the effect of random variation in birth weight caused by small numbers, a locally weighted scatterplot smoother was fitted to follow the individual birth weights for gestational age assuming a normal distribution (Cleveland 1979).

4.3.2 Longitudinal data analysis (I, II)

Random coefficient models were used to model the longitudinal weight and height measurements (Longford 1993). In these models each individual was assumed to follow his or her own growth trajectory, represented by a quadratic or cubic curve. The shape and intercept of the mean profiles were allowed to differ according to case/control status and values of potential confounding factors. Initially a cubic response was fitted to each average trajectory and this was simplified to a quadratic, linear or constant trajectory, if the higher order terms were found to be non-significant ($p \geq 0.05$). In Study II, separate

models were fitted for three age periods: 1) 0–1.9 years, 2) 2–9.9 years, and 3) ≥ 10 years in order to allow the use of simple polynomial models to represent the age trajectories of individuals. In order to take into account the effect of introduction of infant formula or solid food on growth (I), the pattern of development representing average weight was allowed to change if there was at least 1 month from the start of supplementary feeding.

The effect of weight or height on the risk of type 1 diabetes was evaluated using logistic regression. In Study I the weight at a given age was obtained from the estimated individual growth trajectories obtained from random effects models described above. When used for estimating individual values, the models did not include covariates. To obtain estimates for relative weight and height at particular ages in Study II, a separate cubic spline smoother was fitted to the observations from each individual and used to interpolate at the appropriate ages (Green and Silverman 1994).

4.3.3 Analysis of incidence rates (III, IV)

Incidence rates for the development of type 1 diabetes were calculated from the diagnosis of type 1 diabetes in the index child (III), or from birth (IV). The incidence rates were also stratified by the levels of exposures of interest as well as by potential confounding factors.

To evaluate the effect of the exposures of interest on the risk of type 1 diabetes, single and multiple term analyses were carried out using appropriate applications of generalized linear models (McCullagh and Nelder 1989). Log-linear Poisson models were fitted in the whole population of initially disease-free siblings to their incidence rate of type 1 diabetes during the follow-up (III). In order to take into account the dependence of the observations of children coming from the same family in the Poisson regression analysis, parameters were estimated by the generalized estimating equation approach (Diggle et al. 1994), and robust standard errors used in obtaining the 95% confidence intervals (95%CI). Cox proportional hazards model (Cox and Oakes 1984) using age as the main time scale in all the analysis was used in evaluating the effect of vitamin D on the risk of type 1 diabetes (IV).

5 Results

5.1 Growth and the risk of type 1 diabetes

5.1.1 *Infancy (I)*

There was some indication of greater weight and length during the first year of life in children who developed type 1 diabetes compared to the controls (Figure 2). The fitted patterns for the difference in weight and length between the case and the control children were very similar. The final model indicated a constant difference between the case and the control boys during the first year of life, and for both weight and length was on the borderline of statistical significance ($p=0.09$, and $p=0.07$, for the difference in the intercepts, respectively). For girls, the weight and length increment was greater in the cases than in the controls until approximately 7 months of age according to the final model.

5.1.2 *Childhood (II)*

Both boys and girls who developed type 1 diabetes were observed to be heavier than control children from early infancy onwards (Figure 3). Before 2 years of age, the fitted difference in relative weight between the case and the control children in the final model was constant for both boys and girls ($p=0.09$, and $p=0.01$, respectively). From 2 to 9.9 years of age the model indicated no changes in the estimated mean difference in relative weight between the case and the control boys. Among girls, relative weight was observed to be increasing in the cases compared to the controls from 4 to 8 years of age according to the final model.

For relative height there was a clear difference between the case and the control boys from early infancy onwards (Figure 3). The fitted difference in relative height between case and control girls was observed to develop during the first 6 months of life, after which it remained stable. There was a limited amount of information available from the age of 10 years onwards, especially for girls, and only the difference in relative height between the case and the control boys was found to be statistically significant.

In Figure 4, the association between relative weight and relative height with the risk of type 1 diabetes is presented.

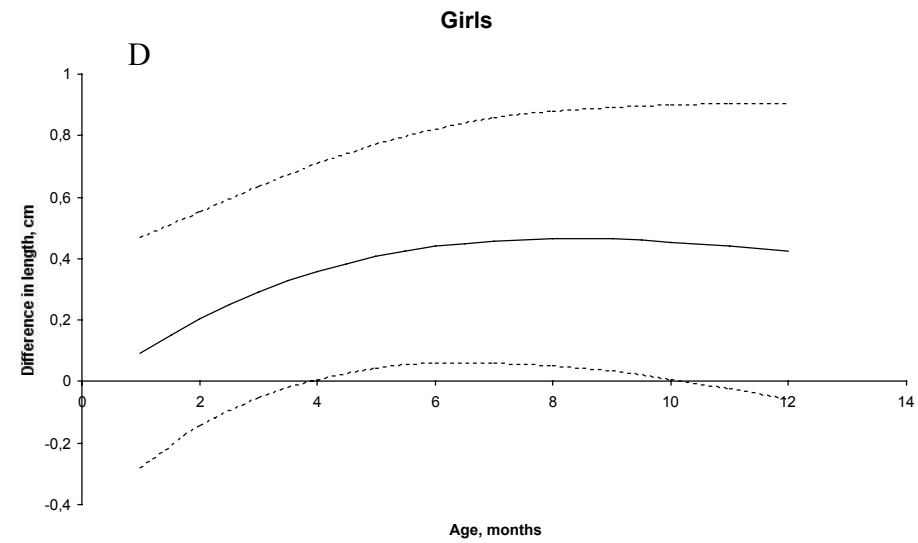
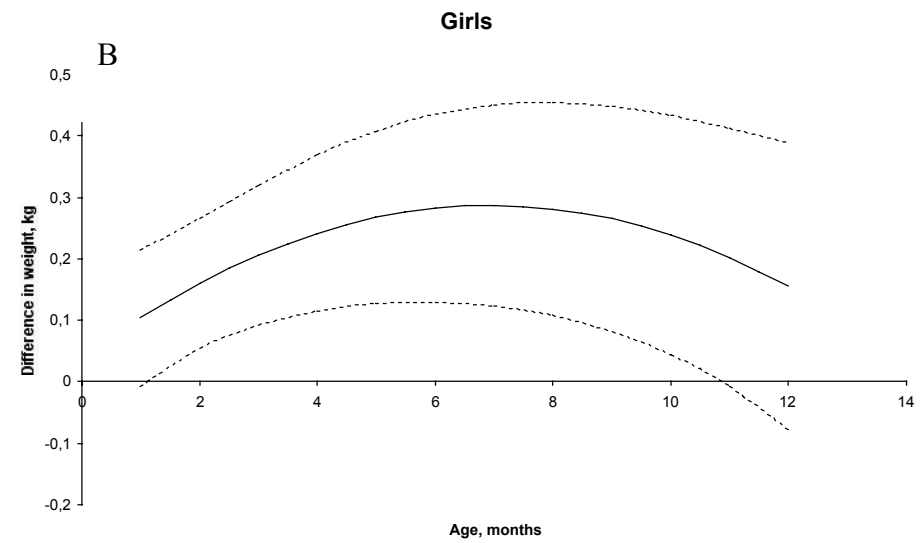
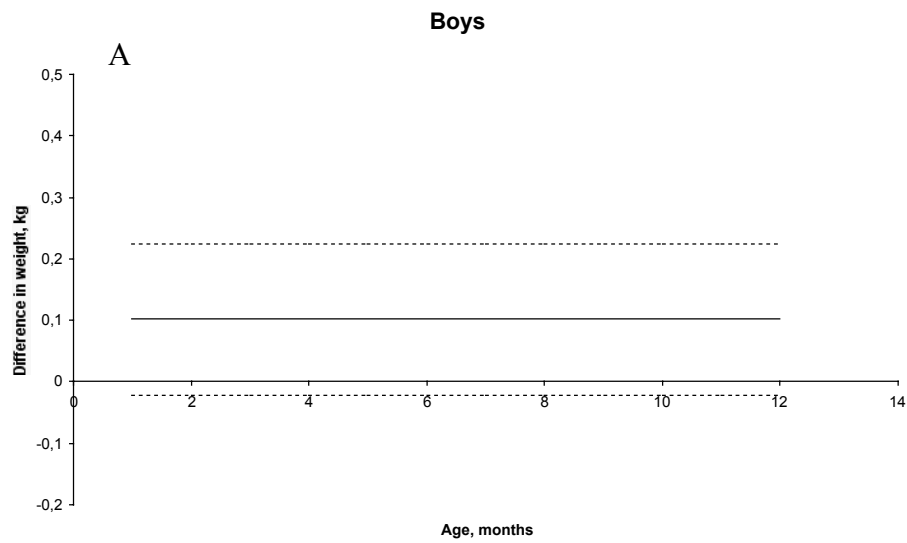


Figure 2. Estimated difference in weight [A) boys, B) girls] and length [C) boys, D) girls] between the case and the control children during the first year of life from the fitted random coefficient regression models in the Childhood Diabetes in Finland Case-Control Study. 95% confidence intervals for the difference are indicated with dashed lines.

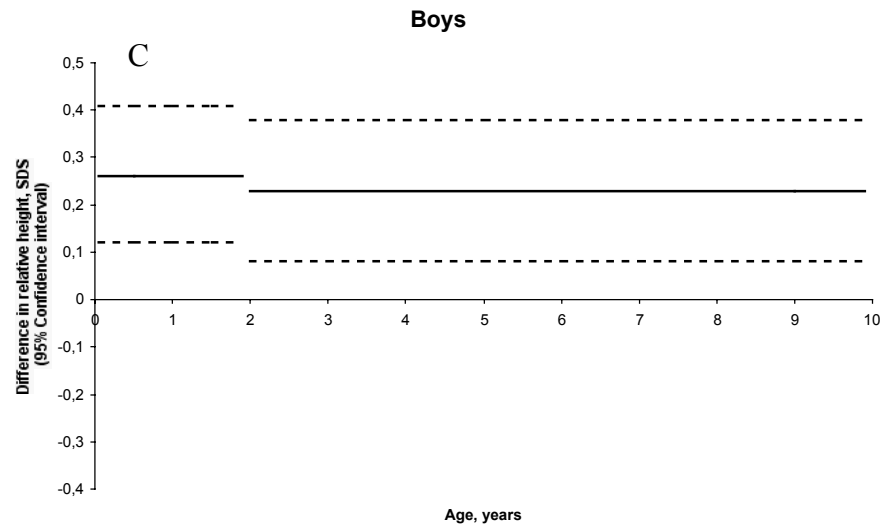
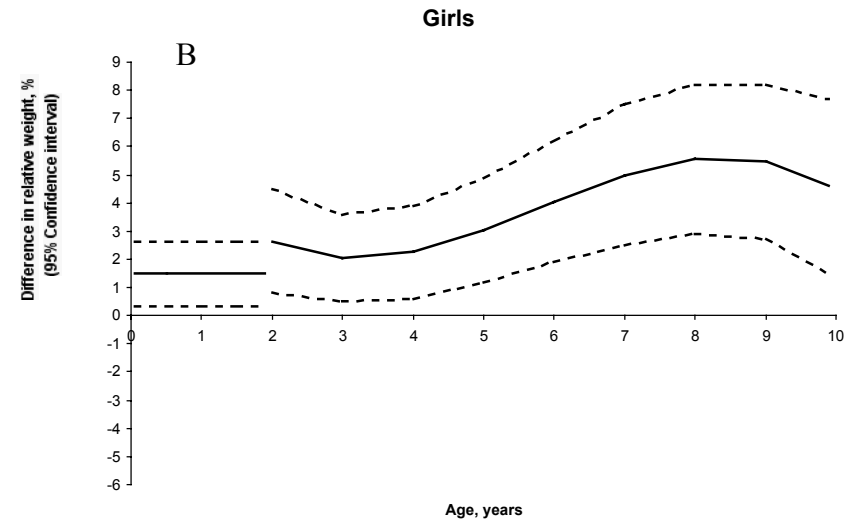


Figure 3. Estimated difference in weight [A) boys, B) girls] and height [C) boys, D) girls] between the case and the control children from the fitted random coefficient regression models in the Childhood Diabetes in Finland Case-Control Study. Separate models used for 0 to 1.9, and 2 to 9.9 years of age. 95% confidence intervals for the difference are indicated with dashed lines.

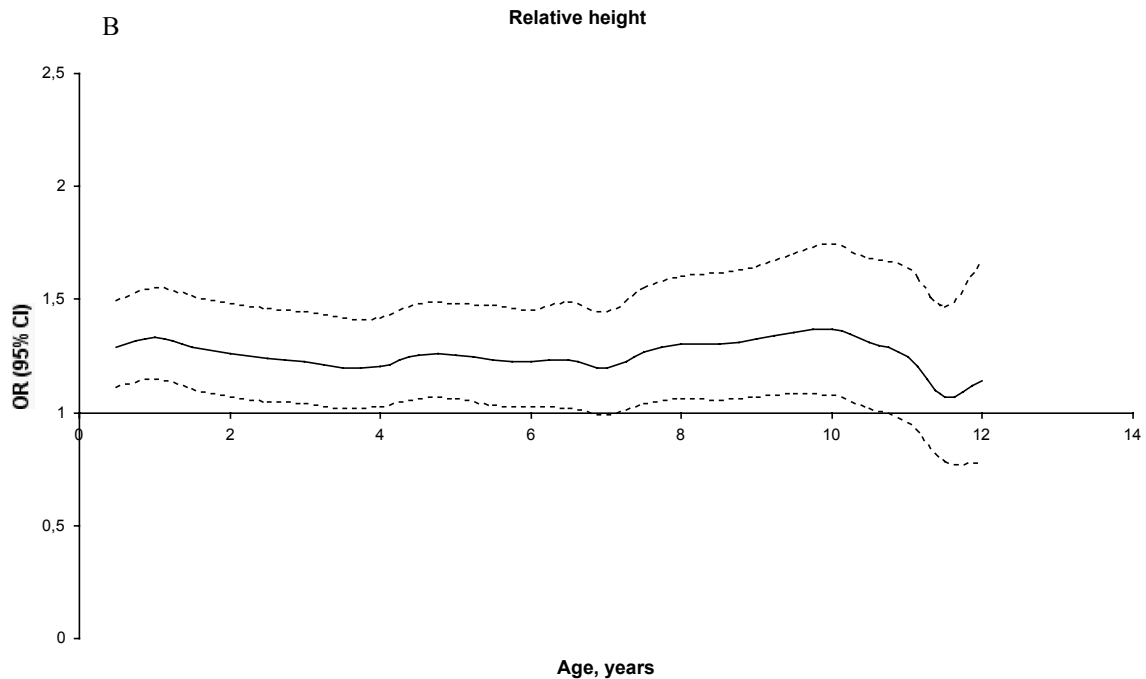
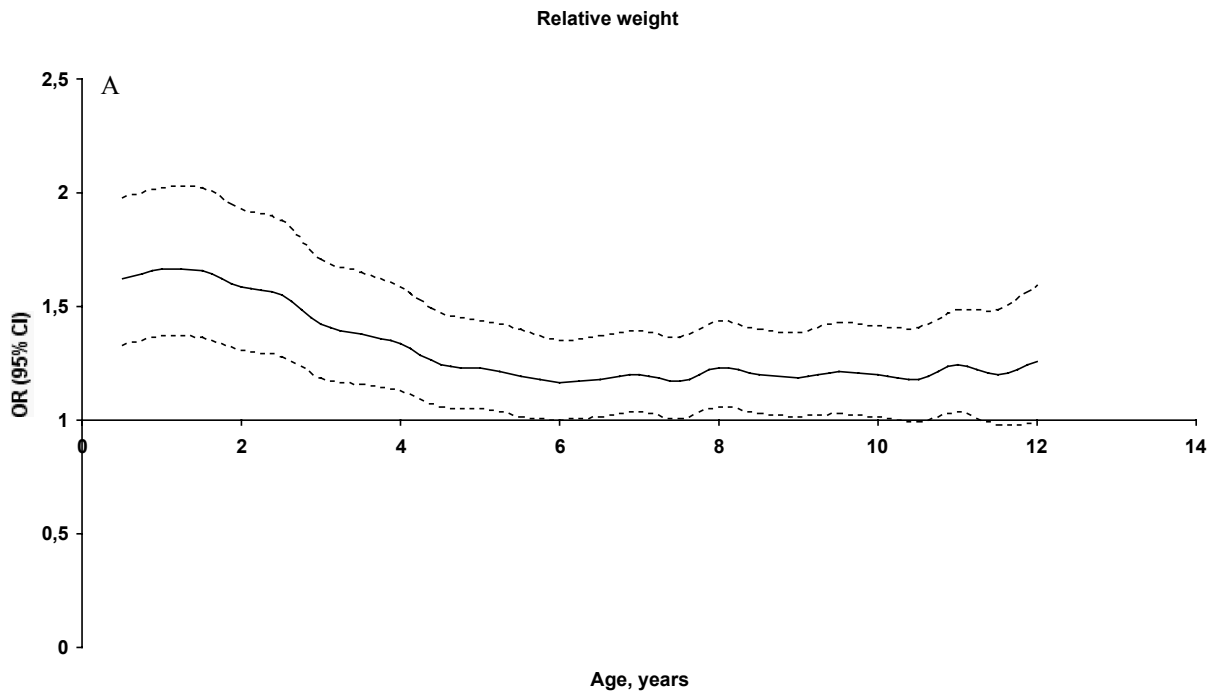


Figure 4. Risk of type 1 diabetes for an increase of 10%-units in relative weight (A) and for a 1 SDS increase in relative height (B) in the Childhood Diabetes in Finland Case-Control Study. Adjusted for sex, date of birth, and the corresponding value of the other anthropometric measure. Dashed lines indicate the 95% confidence limits for the odds ratio.

5.1.3 Target height (II)

There was slight suggestion of an association between the target height calculated from the heights of the parents and the risk of type 1 diabetes (OR 1.2, 95% CI 0.99–1.5, $p=0.06$). However, no evidence for an association between target height and the risk of type 1 diabetes was present after adjustment for child's own height at any age (OR 0.7–1.1, $p \geq 0.38$). Adjustment for target height did not affect the association between child's own height and risk of type 1 diabetes.

5.2 Dietary factors and the risk of type 1 diabetes

5.2.1 Infant feeding and cow's milk consumption (I, III)

The results from the DiMe Sibling Cohort Study (III) were inconclusive regarding to infant feeding and the risk of developing type 1 diabetes (Table 2). There was some suggestion of a slightly greater incidence of type 1 diabetes among those children who were exposed to cow's milk products before 2 months of age, as well as for those breast fed for less than 2 months, although these associations were not statistically significant.

The incidence of type 1 diabetes was somewhat greater for those children consuming at least three glasses of milk and/or sour milk per day compared to those drinking less than that (III, Table 2). A similar difference in the incidence of type 1 diabetes was observed when the daily consumers of milk were compared with non-consumers (rate 64 vs. 13 per 10,000 years at risk, respectively). Due to small number of exposed siblings, evidence for the association between daily consumption of sour milk and the incidence of type 1 diabetes remained inconclusive (rate 63 vs. 56 per 10,000 years at risk, for users and non-users, respectively).

Table 2. Incidence and hazard of type 1 diabetes by infant feeding and childhood milk consumption in the Childhood Diabetes in Finland Sibling Cohort Study.

	Number of cases	Time at risk, years	Incidence /10,000 years at risk	Adjusted for sex, age, maternal age and education HR (95% CI)	Adjusted in addition for other variables in table HR (95% CI)
Total duration of breast-feeding (months)					
<2	5	703	71	1 (reference)	1 (reference)
≥2	28	4,404	64	0.49 (0.2–1.3)	0.53 (0.2–1.6)
Missing	0	346	0		
Age at introduction of milk supplements (months)					
≥2	21	3,714	57	1 (reference)	1 (reference)
<2	9	1,163	77	1.88 (0.7–4.9)	1.44 (0.5–4.2)
Missing	3	346	53		
Childhood milk and sour milk consumption (glass per day)					
< 3	4	1,872	21	1(reference)	1 (reference)
≥ 3	27	3,546	76	3.11 (1.1–9.3)	2.75 (0.9–8.4)
Missing	2	36	555		

5.2.2 Vitamin D (IV)

Incidence of type 1 diabetes was observed to be consistently higher for those children having low intake of vitamin D supplementation or indication of rickets during the first year of life (IV, Table 3). Among children who had received vitamin D supplementation regularly, the risk was estimated to be reduced by 80% if the child had received at least the recommended dose of Vitamin D (2000 IU) when compared to those having received doses less than that. These associations between indicators of vitamin D intake and status with the risk of type 1 diabetes were not affected by adjustment for neonatal or social characteristics. Adjustment for the increased dose of vitamin D supplementation, strengthened the association between indicated rickets and the risk of type 1 diabetes.

Table 3. Incidence and hazard of type 1 diabetes by the use of vitamin D supplements and suspected rickets in infancy in Northern-Finland Cohort 1966 Study.

	Number of cases	Time at risk, years	Incidence /10,000 years at risk	Adjusted for sex, neonatal and social factors ¹	Adjusted in addition for standardized growth rate and birth weight
				HR (95% CI)	HR (95% CI)
Use of vitamin D supplements					
Not at all	2	981	20.4	1 (reference)	1 (reference)
Irregularly	12	36,143	3.3	0.16 (0.04–0.74)	0.16 (0.04–0.74)
Regularly	67	276,235	2.4	0.12 (0.03–0.50)	0.12 (0.03–0.51)
Dose of Vitamin D ²					
Low	2	2,093	9.6	1 (reference)	1 (reference)
Recommended	65	273,024	2.4	0.22 (0.05–0.90)	0.21 (0.05–0.88)
Suspected rickets					
No	77	306,944	2.5	1 (reference)	1 (reference)
Yes	4	6,414	6.2	2.9 (1.0–8.7)	3.0 (1.0–9.0)
Overall adequacy of Vitamin D ³					
Yes	72	303,212	2.4	1 (reference)	1 (reference)
No	9	10,147	8.9	4.5 (2.1–9.4)	4.7 (2.12–9.8)

¹ Adjusted for sex, gestational and maternal age, parity, length of maternal education, and social status. Suspected rickets and overall adequacy of vitamin D adjusted in addition for increased dose of vitamin D.

² The effect of dose shown for those children who had received vitamin D supplementation regularly, recommended dose ≥ 2000 IU/day.

³ Inadequacy determined on the basis of intake of vitamin D supplementation (receiving none, or low dose of vitamin D) or by the presence of suspected rickets.

5.3 Confounding and effect modification of growth and nutrition in infancy in relation to the risk of type 1 diabetes (II, IV)

In the longitudinal data analysis, children who had been formula fed for at least 1 month, were observed to be heavier than the breast fed children (II). No difference in the estimated effect of formula feeding on growth was found between the case and the control children (test for interaction $p=0.63$, and $p=0.14$, for boys and girls, respectively). The final model indicated a constant difference of 42 grams (95% CI 5–79 grams, $p=0.02$) between boys who had been formula fed for at least 1 month prior to the weight measurement and the breast-fed boys of the same age. The formula-fed girls were consistently heavier than the breast-fed girls from 4 months of age (difference at 4 months 72 grams, 95% CI 28–116 grams, $p=0.001$).

Adjustment for the individual weight gain curve had no effect on the association between an early age at the introduction of formula feeding (< 3 vs. \geq 3 months) and the risk of type 1 diabetes (adjusted OR 1.5, 95% CI 1.1–2.2). The association between increased weight and the risk of type 1 diabetes remained after adjustment for early introduction of formula feeding, and no evidence for interaction was observed between these two risk factors in relation to the risk of type 1 diabetes (Table 4).

Average standardized growth rate was observed to be somewhat lower in children who were reported not to have received any vitamin D supplementation in infancy compared to others ($p=0.13$ for weight, and $p<0.002$ for length, Table 5). Dosage of vitamin D did not have a marked effect on growth rate in those children who received vitamin D supplementation regularly. There was some suggestion of slower growth in weight among children suspected of having rickets ($p=0.10$) or some indication of inadequate vitamin D intake or status during the first year of life ($p=0.04$).

In the multiple term Cox regression analysis, adjustment for standardized growth rate or birth weight slightly strengthened the association between suspected rickets and type 1 diabetes, but did not have a marked effect on estimates of intake of vitamin D supplementation (Table 3). Adjusting for the indicator of adequacy of vitamin D intake did not have an effect on the estimates of standardized growth rate (data not shown). Among children whose growth rate during the first year of life was either 1 SDS below or above the average for the corresponding age, there was some suggestion for a greater importance of adequate vitamin D supplementation (Table 6), although the statistical test for interaction did not indicate a differing effect ($p= 0.68$).

Table 4. Joint effect of weight at 6 months of age and the age at introduction of formula feeding in relation to the- risk of type 1 diabetes in the Childhood Diabetes in Finland Case-Control Study.

Age at introduction of formula feeding	Weight at 6 months ¹	Observed OR (95% CI)	Expected ² OR
\geq 3 months	Quartile 1	1 (reference)	1
\geq 3 months	Quartile 2–3	1.6 (1.0–2.6)	1.6
\geq 3 months	Quartile 4	1.9 (1.1–3.2)	1.9
< 3 months	Quartile 1	1.6 (0.7–3.7)	1.5
< 3 months	Quartile 2–3	2.3 (1.3–3.2)	2.4
< 3 months	Quartile 4	3.2 (1.7–6.0)	2.9

¹ Quartiles of weight at 6 months, have been determined using the sex specific values from the control children.

² Expected values calculated on the basis of a model where the terms were adjusted for each other

Table 5. Mean standardized growth rate in infancy by indicators of vitamin D intake and status in the Northern-Finland Cohort 1966 Study.

	N ¹	Standardised growth rate	
		Weight mean (SD)	Length mean (SD)
Use of vitamin D supplements			
Not at all	30/28	-0.33 (0.7)	-0.38 (0.88)
Irregularly	1,085/1,077	0.02 (1.0)	-0.08 (1.0)
Regularly	8,523/8,418	-0.00 (1.0)	0.01 (1.0)
Dose of Vitamin D ²			
Low	65/64	-0.05 (1.2)	-0.06 (1.2)
Recommended	8,427/8,326	-0.00 (1.0)	0.01 (1.1)
Suspected rickets			
No	9,438/9,324	0.00 (1.0)	-0.00 (1.0)
Yes	200/199	-0.11 (1.0)	0.01 (1.1)
Overall adequacy of Vitamin D ³			
Yes	9,323/9,212	0.00 (1.0)	0.00 (1.0)
No	315/311	-0.11 (1.0)	-0.03 (1.1)

¹ number of subjects with growth rate in weight/length available.

² Shown for those children only receiving vitamin D supplement regularly, recommended dose \geq 2000 IU/day.

³ Inadequacy determined on the basis of intake of vitamin D supplementation (receiving none, or low dose of vitamin D) or by the presence of suspected rickets.

Table 6. Joint effect of growth rate in infancy and the adequacy of vitamin D supplementation in relation to the risk of type 1 diabetes in the Northern-Finland Cohort 1966 Study.

Adequate vitamin D ¹	Growth rate, SDS	Observed HR (95% CI)	Expected ² HR
Yes	<-1	1 (reference)	1
Yes	-1 to 1	1.5 (0.7-3.3)	1.3
Yes	> 1	1.8 (0.7-4.6)	1.7
No	<-1	7.1 (1.5-34)	3.9
No	-1 to 1	4.8 (1.5-15)	5.1
No	> 1	8.1 (1.7-39)	6.5

¹ Inadequacy determined on the basis of intake of vitamin D supplementation (receiving none, or low dose of vitamin D) or by the presence of suspected rickets.

² Expected values calculated on the basis of a model where the terms were adjusted for each other.

6 Discussion

6.1 Study design

In this thesis, data are presented from one case-control study (I, II) and from two cohort studies (III, IV). All study designs used in epidemiology have their strengths and weaknesses, which largely differ between case-control and cohort design.

Case-control study The main problems with case-control studies are usually related to bias in obtaining information (e.g. recall or reporter bias) or to selection of participants. As the individual growth charts were obtained from child welfare centres and school health care units, and recorded years before the diagnosis of the disease, it is difficult to see how the growth data used in Studies I and II could be materially affected with information bias. The existence of recall bias in obtaining information on infant feeding patterns in the DiMe Case-Control study (I) seems somewhat more probable. However, at the time of the study in the late 1980s, the hypothesis of the effect of infant feeding on subsequent development of type 1 diabetes was not widely known. As no difference was found between the case and the control children in the reported age at introduction of solid foods or in the overall duration of breast-feeding, it does not seem likely that the observed difference in the age at introduction of cow's milk formula feeding would be solely a result from a recall bias.

The existence of a selection bias in the DiMe Case-Control Study (I,II) would seem slightly more worrying, as up to three rounds were carried out for the selection of the control children. A shorter duration of the length of education of the mothers of the case children when compared to those of the controls, has been previously reported from the current series (Virtanen et al. 1993), as well as from several other case-control studies (Blom et al. 1989, McKinney et al. 2000). As well-educated people are known to be more willing to participate in scientific studies, this difference could be accounted for a differential selection of case and control children. However, it is also possible that maternal education is a potential confounder, representing a proxy marker for some risk factor of type 1 diabetes (e.g. hygiene, childhood nutrition). The existence of selection bias was assessed by comparing the prevalence of obesity in the DiMe Case-Control Study with that seen in the large Cardiovascular Risk in Young Finns study in the 1980s (Table 7). The proportion of obese control children was slightly higher than expected in young boys and slightly lower in girls, but the prevalence of obesity in the case children was consistently higher than earlier observed in the unaffected children (Nuutinen et al. 1991). Also in the multiple term analyses, the significant association between obesity,

Table 7. Prevalence of obesity (%) in the Childhood Diabetes in Finland Case-Control study¹ and in the Cardiovascular Risk in Young Finns Study² using U.S. reference values³.

	Present study ³		Cardiovascular Risk in Young Finns study				
	N	CASE % obese (95% CI)	N	CONTROL % obese (95% CI)	1980 % obese (95% CI)	1983 % obese (95% CI)	1986 % obese (95% CI)
Boys							
6 yrs	159	10.9 (6.0–15.8)	296	9.1 (6.1–13.0)	7.6 (4.7–11.6)	6.3 (3.6–10.3)	-
9 yrs	91	8.8 (3.9–16.6)	256	6.6 (3.9–10.4)	5.3 (3.1–8.5)	7.5 (4.5–11.8)	6.3 (3.5–10.3)
12 yrs	12	10.5 (1.3–33.1)	163	6.1 (3.0–11.0)	3.4 (1.7–6.1)	5.8 (3.4–9.4)	6.4 (3.6–10.5)
Girls							
6 yrs	154	24.0 (17.3–30.8)	259	13.5 (9.4–17.7)	17.9 (13–23.4)	17.5 (12.7–23.9)	-
9 yrs	70	12.9 (6.1–23.0)	215	2.8 (1.0–6.0)	3.7 (1.9–6.5)	4.9 (2.6–8.4)	4.9 (2.5–8.6)
12 yrs	14	7.1 (0.2–33.9)	152	1.0 (0.1–3.6)	3.0 (1.5–5.6)	2.9 (1.2–5.7)	2.9 (1.1–5.9)

¹ Nuutinen et al. 1991

² Cronch and Roche 1982

³ Obesity determined for those children having observations from \pm 6 months of the corresponding age.

as well as that of greater weight in infancy or greater relative height in childhood, and an increased risk of type 1 diabetes remained unchanged after adjustment for the length of maternal education as well as for several other potential socio-economic confounders.

Cohort study Type 1 diabetes is a rare disease, and there are few cohort studies investigating its etiology. In this thesis data from two cohorts were used: a cohort of more than 700 siblings of children with diabetes (III), and a large birth cohort comprising of over 10,000 children (IV). Even if the incidence of type 1 diabetes in Finland is higher than anywhere else in the world (Karvonen et al. 2000), and even if the siblings of children with diabetes are likely to be genetically susceptible to type 1 diabetes, the main problem with these studies is still the small number of cases. This decreased the probability of detecting any association between the factors studied even if a real association existed (i.e. Type II error). As a result from small numbers of cases, the observed effect estimates were imprecise. This was clearly evident in the wide confidence intervals for the effect of vitamin D supplementation (IV), as well as that of childhood milk consumption (III) on the risk of type 1 diabetes.

Another problem common to cohort studies is related to losses to follow-up. In the study investigating the association between vitamin D and the subsequent risk of type 1 diabetes (IV), not all the mothers attended the 1 year follow-up visit. It is possible that these non-participants were also less active in giving vitamin D supplementation to their children than those continuing in the study. Hypothetically this could lead to a slight underestimation of the incidence rates of type 1 diabetes. Losses to follow-up after obtaining information on the use of vitamin D supplementation have been minimal and mainly due to emigration of the study participants, as the information on the outcome was obtained by record linkage without a need for personal contact. An exact date of emigration was not known for a proportion of those that had migrated during the study, and had to be estimated, which has led to a small imprecision in the calculation of the overall time at risk. On the whole, the proportion of the non-participants as well as those that migrated was very small, so their effect on the results is probably negligible. Further it should be noted, that the age-specific incidence rates observed in this study correspond very well to those previously reported for corresponding time period (Karvonen et al. 1999). Losses to follow-up are not likely to have materially influenced the results of the DiMe Sibling Cohort study, as the follow-up period was relatively short and information on diabetes status was obtained by record linkage.

Despite the limitations discussed above, the evidence for the association between the dietary factors studied and subsequent development of type 1 diabetes obtained from the cohort studies included in this thesis is nevertheless valuable. When information is

collected before the onset of the disease of interest, and when there is no need to select subjects, the main sources of bias associated with case-control design may be avoided.

6.2 Longitudinal data analysis

Growth comparisons are still frequently made by comparing mean weights and heights at several time points, despite well known problems with the approach such as the lack of common times of measurement and multiple hypothesis testing (Mathews et al. 1990). To avoid such problems, random coefficient models were used to represent the growth trajectories of the children (I, II) (Longford 1993). In growth reference charts it is intended that normal growth is represented by a straight line (Sorva et al. 1984), which would lead to the use of very simple random slopes models. However, due to a wide within-individual variation, in particular during the periods of extremely fast growth in infancy, extensive smoothing has been carried out in the development of the national growth reference charts (Pere 2000), and there is much individual variation about the resulting standard. This problem was clearly visible in the behaviour of the fitted curves for relative weight and relative height (Figure 5). Even when the data for the case and the control children was modeled separately, the mean behaviour was nearly identical and far from the intended straight line. To accommodate such behaviour in individuals, cubic polynomials were required for satisfactory statistical fit of the overall models.

The presentation of a longitudinal series of measurements as a set of mean values may lead to a severely biased picture of the actual behavior of the measure in time, as mean values are known to be very sensitive to the effect of outlying values (Mathews et al. 1990). A growth profile curve that is based on a set of mean values, will also be excessively affected by the values from subjects with the largest number of measurements when the data are sparse. These problems were evident in the analysis of the present data where the number of individual measurements ranged from 1 to 46, and the overall number of measurements decreased strongly with time. The data also contained two very obese boys who developed diabetes after 13 years of age. By using longitudinal data analysis, it was possible to avoid excessive influence of these individuals. On the basis of the mean curves presented as Figure 1B in Study II, the difference in relative weight between the case and the control boys is increasing

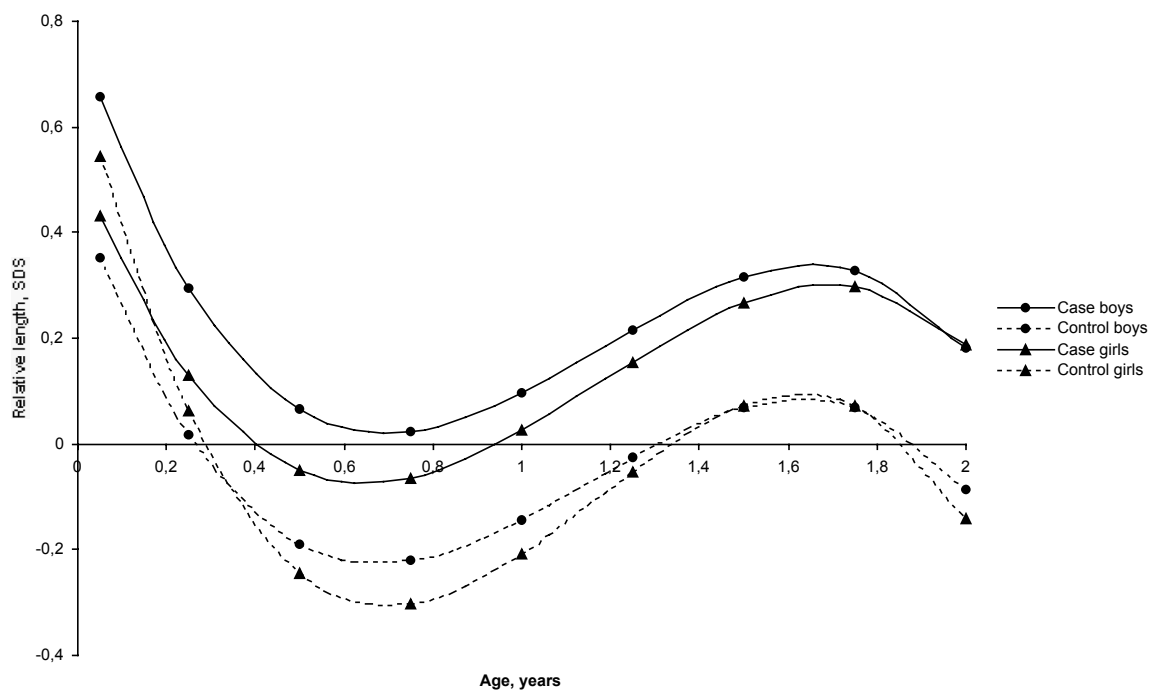


Figure 5. Fitted curves from the cubic random coefficient regression models of relative height for case and control children in the Childhood Diabetes in Finland Case-Control Study.

between 2 and 10 years of age, whereas in the longitudinal data analysis a difference was found only in the intercepts. However, the estimates derived from the longitudinal data analysis are dependent on the choice of polynomial degree. Other modeling strategies could have been used for the data analysis. Using an alternative approach, the shape of the differences between case and control children could have had a different pattern to that presented. It should be noted that the conclusions drawn on the basis of present analysis were found to be insensitive to the choice of polynomial degree, and the same overall picture on the association between relative weight/height and the risk of type 1 diabetes would have been obtained even if the comparison of simple mean values was used.

6.3 Unmatched analyses in the DiMe Case-Control Study

Controls for the affected children in the DiMe Case-Control Study (I,II) were matched for the date of birth and sex. Generally textbooks of epidemiology advice, that when the study design is matched this should be considered in all the statistical analyses and the methods chosen accordingly (e.g. Rothman and Greenland 1998). In this study a decision was made to use unpaired methods of analyses and to include date of birth and sex in all the models as covariates.

Age and sex can be seen as relatively loose criteria for matching. It would have been possible to carry out the longitudinal analysis by using a paired method. However,

this was not done as it was difficult to justify how a growth profile of an individual child should depend upon a growth profile of the respective matched pair. Further, restriction to the paired data in the setting of Study II, would have led to a loss of information from 397 children, as growth information was available for only 380 matched pairs. However, the main risk assessment was also carried out using a conditional logistic regression analysis, and the results did not differ materially from those presented.

In case-control studies it is a generally accepted practice to include several controls for one case subject. In the Study II a similar logic was applied, and a decision was made to use all the available measurements from the control children taken before 13 years of age, whereas data from the cases only up to 1 year preceding the diagnosis was used. This led to a more precise estimate of the individual growth pattern for the control children compared to the cases, in particular at the older ages in the range. After the decision was made to ignore matching in the analyses, any 'age at diagnosis' for the control subjects seemed an artificial criterion for omitting measurements. Again it should be noted that the conclusions made on the basis of the longitudinal analyses presented here were identical to those obtained from the matched data alone.

6.4 Growth before the onset of type 1 diabetes

In this study, increased growth from early infancy onwards was observed to be associated with a greater risk of developing type 1 diabetes. The observation for an association between greater weight in infancy (Baum et al. 1975, Johansson et al. 1994, Bruining 2000) or greater height in childhood (Blom et al. 1992, Price and Burden 1992) with an increased risk of type 1 diabetes were in accordance with earlier reports, whereas this was the first study to observe an association between childhood obesity and the subsequent risk of type 1 diabetes.

Similar mechanisms could underlie the association of both weight and height with the risk of type 1 diabetes. On the basis of epidemiological studies, it is impossible to state whether the observation of increased growth before the diagnosis of type 1 diabetes results from excessive energy intake and thus reflects the effect of an environmental risk factor, or if it is solely a marker of an ongoing disease process. If the basic mechanism was greater vulnerability of the beta-cells resulting from an increased need for production of insulin (Nerup et al. 1988) (stimulated by excessive energy intake), then it could be assumed that greater weight/obesity and faster growth could at least accelerate the ongoing pathogenic process leading to the development of type 1 diabetes. However, if the ongoing autoimmune destruction of the insulin producing

beta-cells leads to increased insulin production as has been suggested (Blom et al. 1992), this could lead to accelerated growth as well as to a tendency for these children to become obese, at least if the insulin sensitivity in peripheral tissues remained normal.

It is possible that the observed association between obesity and increased growth with the risk of type 1 diabetes results from some shared genetic factors rather than environmental effects. Although there was a slight suggestion of greater target height in children who develop type 1 diabetes (II), no effect of parental height or target height was observed when adjusted for child's own height. However, information on the tempo of growth in parents was not available, so it could be that genetically determined rapid growth is underlying the observed association between greater relative height and the increased risk of type 1 diabetes.

6.5 Diet in the development of type 1 diabetes

In the DiMe Sibling Cohort, no convincing evidence was found for an association between an early introduction of cow's milk formula feeding and subsequent development of type 1 diabetes. Although still under debate, such an association has been observed in a large number of case-control studies (Gerstein 1994, Norris and Scott 1996). The observed estimate for the effect of exposure to cow's milk formula feeding before the age of 3 months in the DiMe Sibling Cohort Study, was very close to that found in the earlier case-control studies, although the confidence limits for the estimate were wide. With the limited number of incident cases of type 1 diabetes in the DiMe Sibling Cohort Study, the power of the study would not have been sufficient to detect such a small effect. According to a sample size calculation, the observed number of cases of type 1 diabetes would have been required to be over ten-fold to what was observed in order to detect such a difference at a significance level of 0.05 with a power of 80%.

The observed association between childhood milk consumption and subsequent development of type 1 diabetes observed in the DiMe Sibling Cohort Study remains suggestive. Evidence from earlier case-control studies is controversial (Dahlquist et al. 1990, Verge et al. 1994, Virtanen et al. 1994). It is clear that evaluating the effect of any liquid on the risk of a disease for which symptoms include increased feeling of thirst, is naturally quite problematic with such a design. This may have been an issue in the current study due to difficulties in defining the period of duration of symptoms for each individual. However, analyses restricted to those siblings developing type 1 diabetes at least 1 or 2 years after the index case gave essentially identical results to those presented here (data not shown).

Observations from the population based Northern-Finland Cohort 1966 Study, confirmed the earlier finding of smaller risk of type 1 diabetes for those receiving vitamin D supplementation in infancy compared to others (EURODIAB ACE Study Substudy 2 1999). What was striking in the association between vitamin D and type 1 diabetes in the present study, was the consistency of association through all indicators of vitamin D intake and status. Further, the effect estimates behaved logically in all situations, such that e.g. adjustment for an increased dose of vitamin D supplementation (most likely given as a treatment for the condition) strengthened the association between suspicion of rickets and type 1 diabetes. Also at least slightly stronger effects were observed for either rickets or vitamin D supplementation, when stratification for the other factor was carried out. Although there are several limitations to our study including imprecise effect estimates caused by the relatively small size of the study, as well as in many ways sub-optimal measurement of the exposure status, the results still strongly support further evaluation of the effect of ensuring adequate vitamin D intake on the subsequent risk of type 1 diabetes.

There are several potential mechanisms that describe how nutritional exposures could affect the risk of type 1 diabetes, these are discussed in more detail in the literature review (section 2.2.3). However, children's dietary intakes are known to be associated with family's social position (Laitinen et al. 1995). Evidence for social differences e.g. in the pattern of giving vitamin D supplementation to infants was also obtained in the present study. However, adjustment for several social indicators had a negligible effect on the observed associations between dietary indicators and the risk of type 1 diabetes.

6.6 Confounding and effect modification by nutrition and growth in infancy in relation to the risk of type 1 diabetes

It has been suggested that the association between an early introduction of cow's milk formula feeding and an increased risk of type 1 diabetes (Gerstein 1994) is mediated by the effects of feeding on growth (Johansson et al. 1994). Those children who are formula fed tend to grow faster than those who are not (Salmenperä et al. 1985). If indeed increased growth in infancy was on the causal pathway between formula feeding and the risk of type 1 diabetes, adjustment for the effect of growth would have been expected to attenuate the effect of formula feeding. This was not observed in the present study (I), neither was the estimated effect of formula feeding found to differ according to levels of early growth. It would therefore seem that both infant feeding and early growth may have an independent role in the development of type 1 diabetes.

The putative causal triangle between vitamin D, growth, and the risk of type 1 diabetes provides a text book example of confounding. A poor vitamin D status is known to reduce growth, and potentially to increase the risk of diabetes, whereas greater growth has been associated with an increased risk of type 1 diabetes. Adjustment for the effect of each other when evaluating the effect of vitamin D or growth on the risk of type 1 diabetes, would therefore be expected to increase the absolute magnitude of the estimates. The strengthening of the effect by adjustment of adequacy of vitamin D intake/status and early growth rate for each other in the Northern-Finland Cohort 1966 Study was very small. This may be due to the relatively small size of the key exposure groups, problems in classifying the exposed individuals, as well as the severity of vitamin D deficiency needed to decrease the growth rate. It seems possible that the body may be able to maintain vitamin D at a level sufficient for normal growth, although the levels of might be sub-optimal for other metabolic functions. Although several indicators of vitamin D intake and status were available in the Northern-Finland Cohort 1966 Study, they are all relatively rough and do not indicate the actual severity of vitamin D inadequacy.

Statistical tests for interaction are known to have considerably lower power than those for corresponding main effects. Given the small size of the study, no final conclusions about the interaction between adequacy of vitamin D intake/status and growth rate in infancy in relation to the risk of type 1 diabetes can be made on the basis of the present analyses. However, the results seem to suggest that there might be a greater effect of adequacy of vitamin D intake/status both for those with low and high growth rate, when compared to children growing as expected. A low growth rate in a child classified as having inadequate vitamin D supplementation could be seen as an indicator of the severity of vitamin D deficiency. However, it is also possible that in this group, misclassification of the exposure is smaller than in the other groups, and thus the effect of vitamin D is observed to be more pronounced than expected on the basis of the adjusted analysis. Also, the interaction analysis seemed to suggest a greater risk of type 1 diabetes than expected for the combination of inadequate intake of vitamin D and fast growth during the first year of life. If this is true, given the greater probability of misclassification by the vitamin D inadequacy in the fast growing group, this could be seen to indicate a marked effect, even for a relatively mild inadequacy of vitamin D status on the risk of type 1 diabetes.

6.7 The public health view

When studying the effects of environmental factors on the development of type 1 diabetes, it is important to try and relate the changes in the exposure at the population level with the steeply increasing incidence of type 1 diabetes. Although not all external factors affecting the pathogenic process leading to the development of a disease are necessarily associated with the increase in its incidence, this approach might give us a better idea what actually could be done in order to at least slow down this deleterious development. However, during past decades changes in the environment have been manifold, and it seems that this theoretical approach is not able to substantially narrow down the multiplicity of hypotheses about the effect of environment on the risk of type 1 diabetes.

Although the incidence of rickets is still much lower than half a century ago, an increase in its incidence during the 1980s was observed in Finland (Ala-Houhala et al. 1995). The recommended dose of vitamin D supplementation has been reduced to a tenth of the level recommended in the early 1960s (Halman et al. 1964, National Research Council 1989). There is also some indication for a lower compliance in giving vitamin D supplementation to infants in Finland in the early 1990s when compared to that observed in the 1966 cohort. In the STRIP Baby intervention study (1991–1993), 93% of 1-year-olds were using vitamin D supplementation (Langstrom et al. 1997). According to a small survey carried out in Finland in 1993, 65% of the 138 under 2-year-old children had received vitamin D supplementation regularly (Sihvola 1994). The corresponding proportions in the Northern-Finland Cohort 1966 Study were 99.7% and 88%, respectively. Therefore, it seems plausible that the constant increase in the incidence of type 1 diabetes observed in Finland during the past decades, could also be related to the combination of changes in the recommendations of vitamin D supplementation, and compliance in giving the supplementation to the infants. However, the secular increase in growth (Hauspie et al. 1997), and the observed increase in the prevalence of obesity (Porkka et al. 1997, Chinn and Rona 2001) may also be associated with the trend in the incidence of type 1 diabetes. Further, according to the so called hygiene hypothesis, the increase in the incidence of type 1 diabetes could be attributed to improved hygienic conditions in childhood, that has led to a less efficient “education” of the developing immune system during the first years of life (Kolb and Elliott 1994). It should be noted, that these changes that have occurred in the human environment are not independent of each other, and e.g. improved hygienic conditions are likely to have contributed to the secular changes in growth. Another common factor in many of these

secular changes is the increase in the energy intake in relation to energy expenditure, which is already known to contribute to the development of many other diseases.

The public health importance of any dietary factor for the development of type 1 diabetes, depends both upon the frequency of consumption and its diabetogenicity. All the factors investigated in this thesis, are very important because they affect nearly all children in Finland, as well as in other countries. However, type 1 diabetes is still a relatively rare disease, even in Finland which has the highest incidence rates. Therefore, it is evident that any dietary restrictions aimed solely at prevention of type 1 diabetes would benefit only a very small number of genetically susceptible individuals. Given that cow's milk is a major dietary source of calcium and protein in childhood, it is clear, that many more studies are needed to confirm the possible diabetogenicity of cow's milk before any dietary recommendations could be given even to those genetically predisposed. Encouraging breast-feeding (except in some special cases) and preventing obesity are already among the key aims of the general practice in routine child health surveillance. Vitamin D supplementation in Finland is recommended for all the children up to 3 years of age. However, the adequacy of the current recommended dose of vitamin D for infants and children could be questioned. With this exception, most of the conclusions drawn from this study are comforting. It seems that the general nutritional recommendations made for healthy children, are largely relevant for the prevention of childhood diabetes.

7 Summary

The exact pathogenic process leading to the destruction of the insulin secreting beta-cells and further to the development of type 1 diabetes remains only partly understood. However, it is evident that in addition to genetic predisposition exposure to some environmental agents is needed. The purpose this thesis was to evaluate the association between growth and nutrition in infancy and later in childhood with the risk of type 1 diabetes.

The study population of the nation-wide Childhood Diabetes in Finland (DiMe) Case-Control Study was used in evaluating the association between growth and the risk of type 1 diabetes. The DiMe Case-Control Study included all children newly diagnosed with type 1 diabetes, between September 1986 and April 1989, and one control child for each, selected from the Finnish National Population Register. Copies of growth charts and records were obtained from the Child welfare centres and School Health Care Units for 586 case and 571 control children.

In the longitudinal data analysis, both boys and girls who developed type 1 diabetes were observed to be heavier and taller from early infancy onwards compared to the control children. A 10%-unit increment in relative weight was associated with a 50–60% increase in the risk of type 1 diabetes before 3 years of age, and a 20–40% increase from 3 to 10 years of age. The increase in risk of type 1 diabetes for 1 SDS increment in relative height was a 20–30%. Obesity (relative weight >120%) after 3 years of age was associated with a more than two-fold risk of developing type 1 diabetes. It has previously been suggested that the association between the age at introduction of cow's milk formula feeding and the risk of type 1 diabetes is mediated via the effects of feeding on growth. However, according to observations in the DiMe Case-Control Study, both increased growth during the first year of life and young age at introduction of cow's milk formula feeding were independently associated with an increased risk of type 1 diabetes.

Unaffected siblings of the index cases, were invited to participate in the DiMe Sibling Cohort Study. Information on infant feeding and childhood milk consumption was collected from 725 siblings at the time of entry to the study. Thirty-three siblings developed type 1 diabetes by the end of the follow-up in 31st October 1995. Due to relatively small number of siblings developing type 1 diabetes, evidence remained inconclusive with regards to the effect of infant feeding on subsequent risk of type 1 diabetes. There was some indication of an increased risk of type 1 diabetes for those children consuming daily at least three glasses of cow's milk compared to others [hazard ratio (HR) 2.8, 95% CI 0.9–8.4].

The association between vitamin D intake and status with the risk of type 1 diabetes was evaluated in the Northern-Finland 1966 Cohort Study. The birth-cohort consists of all children from the two northernmost provinces of Finland who were due to be born in 1966. During the follow-up until the end of December 1997, 81 subjects had developed diabetes out of the 10,366 with information on supplementation with vitamin D during the first year of life. Regular and irregular vitamin D supplementation were observed to be associated with a reduction in the risk of type 1 diabetes (and HR 0.12, 95%CI 0.03–0.47 and HR 0.16, 95% CI 0.04–0.72, respectively). Also, the dose of vitamin D had a marked effect on the risk of type 1 diabetes. Among those subjects who had received vitamin D supplements regularly but in varying doses, a nearly 80% reduction in the risk of type 1 diabetes was observed compared to those receiving less than recommended (HR 0.21, 95% CI 0.05–0.86). Children who were suspected of having had rickets during the first year of life had a three-fold risk of type 1 diabetes compared to others (95% CI 1.0–9.0).

The most important findings reported in this thesis are the observed decreased risk of type 1 diabetes in children receiving recommended vitamin D supplementation during the first year of life, and the association between greater height and obesity with an increased risk of type 1 diabetes. All of these factors could be linked to the steep increase in the incidence of type 1 diabetes during the past half a century. Increases in the prevalence of obesity and secular growth have occurred in most industrialized countries during the past decades. The recommended dose for supplementation of vitamin D has been reduced in steps to a tenth of the level in the 1960s, and an increase in the incidence of rickets was observed in Finland during the 1980s. As the genetic code changes very slowly in humans, it seems clear that changes in the environment must underlie the trend in the incidence of type 1 diabetes. In order to stop this deleterious development, further studies are warranted to evaluate the effect and safety of vitamin D supplementation and other modifiable environmental factors on the risk of type 1 diabetes.

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Original publications