RISK FACTORS FOR TYPE 1 DIABETES

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SUMMARY

The incidence of type 1 diabetes is increasing at an annual rate of 3%–5%, which suggests a major environmental exposure has changed, by either the gradual introduction of a susceptibility factor or the removal of a protective factor, during the past 60 or more years. Outbreaks and seasonality of type 1 diabetes may suggest an infectious cause, perhaps related to increasing sanitation and loss of herd immunity. Early childhood diet and environmental toxins are also of interest.

Prospective studies following high-risk children from birth to development of the subclinical phase of the disease (islet autoimmunity) and diabetes have been the most reliable source of information regarding risk factors for type 1 diabetes. Prenatal and early post-natal exposures appear to be critical, as the incidence of islet autoimmunity peaks in the second year of life. Among the infectious agents, enteroviral infections (particularly if they are persistent and acquired in early childhood) have gained most interest. Early leads suggesting the role of cow's milk exposure in the initiation of islet autoimmunity have not been confirmed by large prospective studies and a large randomized clinical trial. While numerous studies have reported 1.5–2-fold increases in the risk of islet autoimmunity or type 1 diabetes with various components of early childhood diet and infectious exposures, none of the associations appears particularly strong or universal across different populations.

In the United States, 1 in 300 children and adolescents develop type 1 diabetes by age 20 years, but 1 in 40 offspring of mothers with type 1 diabetes and 1 in 15 offspring of fathers with type 1 diabetes develop type 1 diabetes. The disease is likely caused by the interplay of genetic and environmental factors. Systematic investigation of gene-environment interactions in large, prospectively followed cohorts of young children may help to identify and fully characterize modifiable risk factors and design trials to fully evaluate the strongest candidate triggers of autoimmunity.

INTRODUCTION

The incidence of type 1 diabetes is increasing worldwide, by 3%–5% annually (1), with rates doubling every 20 years (2,3). The rising incidence, outbreaks (4), and a seasonal pattern (5) may suggest that infectious agents play a role in the pathogenesis. However, the incidence has been increasing since at least the 1950s (Figure 11.1) (2,3,6,7,8,9,10,11). Such a secular trend is unlikely to result from a new infectious agent; however, similar to the polio model (12), an "old" microbe could express its diabetogenic effect due to increasing hygiene and decreasing herd immunity. Changes in early childhood diet have also been implicated, as type 1 diabetes has increased the most in the youngest children. Prospective studies (13,14,15) following high-risk children from birth have made important inroads into the understanding of the role of infectious

FIGURE 11.1. Incidence of Type 1 Diabetes Per 100,000 Per Year in Children Age 0–14 Years, 1950–2003
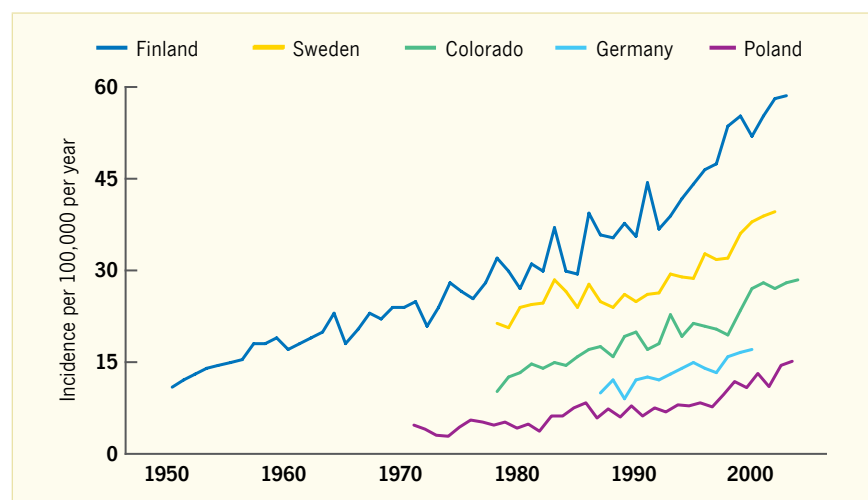

Type 1 diabetes incidence is increasing 3%–5% per year and has doubled every 20 years.

SOURCE: Reference 11. Data for Finland are from the Finnish National Public Health Institute (3); data for Sweden are from the Swedish Childhood Diabetes Registry (6); data for Colorado are from the Colorado IDDM Registry, the Barbara Davis Center for Childhood Diabetes, and SEARCH for Diabetes in Youth (2,7); data for Germany are a compilation of two reports (8,9); data for Poland are from seven regional registries (10).

and dietary factors in type 1 diabetes. Prospective studies have defined two major steps in the pathogenesis of type 1 diabetes (Figure 11.2). Seroconversion to positivity for one or more islet auto-antibodies (to insulin, glutamic acid decarboxylase [GAD], insulinoma antigen 2 [IA-2], or zinc transporter 8 [ZnT8]) marks the development of islet autoimmunity. Approximately 70% of children positive for two or more of these auto-antibodies develop diabetes in 10 years following the appearance of the first auto-antibody (16). In contrast, most children persistently positive for only one islet auto-antibody do not progress to diabetes (16). Data suggest that a variety of exposures may trigger islet autoimmunity, promote progression to clinical diabetes, or affect both of these steps.

Most of the existing data concerning risk factors for islet autoimmunity and type 1 diabetes have come from a handful of prospective studies that have sometimes generated inconsistent results. While the large international prospective cohort study (The Environmental Determinants of

FIGURE 11.2. Two-Step Model of Type 1 Diabetes Development and Potential Role of Environmental Factors
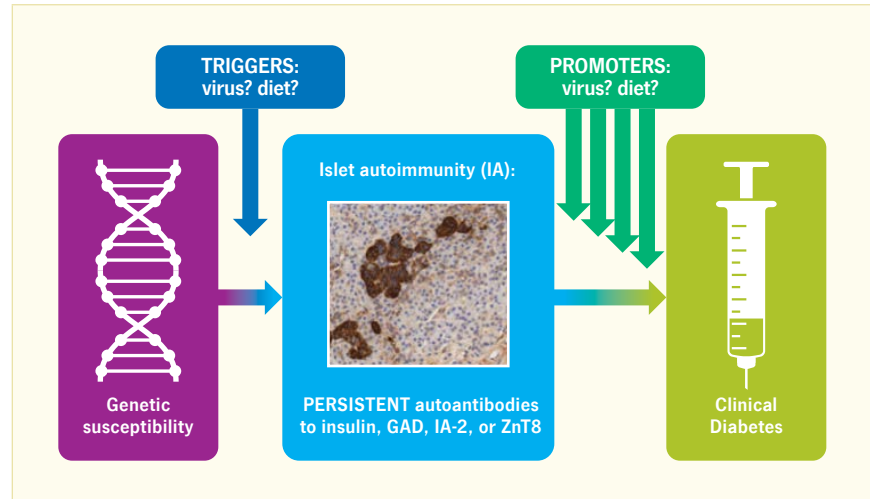
GAD, glutamic acid decarboxylase; IA-2, insulinoma antigen 2; ZnT8, zinc transporter 8.
SOURCE: Original figure constructed by M. Rewers.

Diabetes in the Young [TEDDY]) will likely reconcile some of the inconsistencies, randomized clinical trials of risk factor modifications will provide the ultimate test.

Type 1 diabetes is caused by the interplay of genetic and environmental factors. The genetics of type 1 diabetes is reviewed in depth in Chapter 12 *Genetics of Type 1 Diabetes* and only briefly summarized in the following section. In this chapter, infectious, dietary, and other environmental factors are reviewed in detail, as well as potential gene-environment interactions in type 1 diabetes etiology.

GENETIC FACTORS

FAMILY HISTORY OF TYPE 1 DIABETES

In the United States, approximately 1 in 300 children and adolescents develop type 1 diabetes by age 20 years (Table 11.1) (2,17). The risk is increased to about 1 in 40 in offspring of mothers with type 1 diabetes and 1 in 15 in offspring of fathers affected by type 1 diabetes; the reason for this difference may have an epigenetic origin. The risk to siblings of type 1 diabetes individuals ranges from 1 in 12 to 1 in 35 (18,19). The risk is significantly higher in siblings of individuals diagnosed at age <7 years than in those diagnosed later (20). It is as high as 1 in 3 among monozygotic twins (21). In parents of individuals with type 1 diabetes, the risk by age 40 years is 2.6% and twofold higher in fathers (3.6%) than in mothers (1.7%) (20). By age 60 years, an estimated 10% of first degree relatives will develop type 1 diabetes (22). However, the "familial" cases account for less than 10% of type

TABLE 11.1. Cumulative Incidence, by Age 20 Years, of Type 1 Diabetes and Persistent Islet Autoimmunity in the General U.S. Population and Family Members of Type 1 Diabetes Patients

	TYPE 1 DIABETES	ISLET AUTOIMMUNITY
General population	1:300	1:100
Family members		
Maternal offspring	1:40	1:15
Paternal offspring	1:15	1:5
Siblings (all)	1:12–1:35	1:7
HLA-identical sibling	1:4	1:2
Monozygotic twins	1:3	1:1

HLA, human leukocyte antigen.
SOURCE: References 17, 18, 19, 20, 21, 22, and 23

1 diabetes in the general population; they do not differ from "sporadic" cases in terms of the human leukocyte antigen (HLA)-DR,DQ gene frequencies or the prevalence of islet autoantibodies (23).

Similar to type 1 diabetes, the risk of developing islet autoimmunity varies depending on which relative has type 1 diabetes (Table 11.1). Siblings of type 1 diabetes patients develop islet autoimmunity more frequently than offspring or parents of type 1 diabetes patients (24). The risk of islet autoimmunity is markedly increased if both parents or a parent and a sibling have type 1 diabetes compared with a single affected family member (25).

TABLE 11.2. Proportion of Type 1 Diabetes Subjects With High-Risk HLA Genotypes

POPULATION (REF.)	PERCENT (YEARS COVERED)					P-VALUE
	Before 1975	1975–1999			2000 or Later	
United States (BDC) (39)	38% (1965–1974)	37% (1975–1984)	31% (1985–1994)	26% (1995–2008)		0.02
United States (40)		41% (1978–1988)			28% (2002–2004)	0.05
T1DGC (39)	49% (1965–1974)	45% (1975–1984)	39% (1985–1994)	35% (1995–2008)		<0.0001
Finland (35)	25% (1939–1965)	18% (1990–2001)				0.007
Australia (36)	79% (1950–1969)	60% (1970–1979)	47% (1980–1989)	37% (1990–1999)	28% (2000–2005)	<0.0001
Sweden (37)		36% (1986–1987)	37% (1996–2000)		19% (2003–2005)	<0.0001
Italy (38)		23% (1980–1989)	21% (1990–1999)		27% (2000–2012)	NS
United Kingdom (41)	47% (1922–1946)*	35% (1985–2002)				

High-risk HLA genotypes are defined as DR3-DQ2/DR4-DQ8 (Ref. 41), (DR3)-DQA1*05-DQB1*02/ DRB1*0401-DQB1*0302 (Ref. 35), DRB1*03-DQB1*0201/DRB1*04-DQB1*0302 (Ref. 38), DR3-DQB1*0201/DR4-DQB1*0302 (Ref. 39), DRB1*03-DQB1*02/DRB1*04-DQB1*03 (Ref. 40), DR3/4 (Ref. 36), HLA DQA1*-B1*genotype 0501-0201/0301-0302 (Ref. 37). BDC, Barbara Davis Center for Diabetes; HLA, human leukocyte antigen; NS, nonsignificant; T1DGC, Type 1 Diabetes Genetics Consortium.
* Must have survived 50 years with type 1 diabetes to be tested.
SOURCE: References are listed within the table.

CANDIDATE GENES

The increased risk seen in family members can be attributed to both shared genes and shared environment. The strongest genetic association for type 1 diabetes is with certain alleles of the HLA class II genes (odds ratio [OR] >6). An estimated 30%–50% of the genetic risk for type 1 diabetes is attributable to the HLA region (26). More than 50 confirmed non-HLA loci, found via candidate gene and genome-wide association studies (GWAS), confer the remaining genetic risk, each with modest to small effects (27,28,29,30,31,32). Non-HLA loci most strongly associated with type 1 diabetes include *INS* (33) and *PTPN22* (34), both with an odds ratio of approximately 2. One reason why these genes seem to have relatively small effects is that they may need to work in concert with another factor, such as an environmental exposure (gene-environment interaction), which is covered later in this chapter. The non-HLA gene variants studied more thoroughly so far appear important to both the triggering of islet autoimmunity and to the progression to clinical disease; however, most studies are underpowered to tease out this distinction. (See Chapter 12 for more details on type 1 diabetes genetics.)

INCREASING PENETRANCE OF THE MODERATE-RISK HLA GENOTYPES

Seven studies (35,36,37,38,39,40,41) have explored temporal changes in the frequency and/or distribution of HLA genotypes associated with type 1 diabetes susceptibility. All but one have suggested a decreasing frequency of the highest-risk HLA-DR,DQ genotype over time in individuals diagnosed with type 1 diabetes (Table 11.2) (35,36,37,38,39,40,41). A study conducted in Finland reported a significant decrease in the frequency of the HLA-DRB1*03-DQB1*0201/ DRB1*04-DQB1*0302 genotype from 25.3% to 18.2% over a 62-year time period (35). A similar decrease in the frequency of the highest-risk HLA genotypes (from 47% to 35% over a 50-year time period) was noted in the United Kingdom (41). A study combining the Type 1 Diabetes Genetics Consortium participants and a Colorado clinic population cohort (39) showed a similar linear decrease. Additional evidence for decreasing frequency of the highest-risk genotype was published from Colorado (40), Sweden (37), and Australia (36). The decrease in the frequency of cases with the highest-risk HLA genotype with the corresponding increase in moderate and lower risk genotypes suggests an increasing penetrance of moderate and lower risk HLA genotypes that could be explained by increasing environmental pressure, e.g., higher levels of exposure to the critical factor.

INFECTIOUS AGENTS

Prospective studies of high-risk children have shown that the incidence of islet autoimmunity peaks in the second year of life (42,43,44), suggesting that the putative environmental trigger(s) must occur very early in life in many cases. Therefore, *in utero*, perinatal, or early childhood infections and infant diet are likely candidate exposures.

SEASONALITY OF TYPE 1 DIABETES DIAGNOSIS, ISLET AUTOANTIBODIES, AND BIRTH

Type 1 diabetes incidence in children is higher in autumn-winter and lower in spring-summer in both hemispheres, resembling seasonality of viral infections (7,45,46). However, children age 11–15 years show more obvious seasonal variation compared to children diagnosed before age 5 years (47), which may suggest that additional factors may play a role, e.g., easier detection of the onset of diabetic signs/symptoms in children attending school. Development of islet autoimmunity could also depend on an environmental exposure during pregnancy as suggested by seasonality of islet autoantibodies in cord blood (48) and seasonal distribution of birth dates of type 1 diabetes patients in some populations (49,50).

VIRAL INFECTIONS

Viral infections have long been implicated in the etiology of type 1 diabetes, but a definitive proof has been elusive. Footprints of infectious triggers of islet autoimmunity may be hard to detect due to a long incubation period of type 1 diabetes in most cases. A number of agents have been suggested to trigger autoimmune diabetes; the strongest leads are reviewed in this section.

Enteroviruses have shown associations with type 1 diabetes in both animal and human studies (51,52). These viruses have a tropism to human pancreatic islets *in vivo* and *in vitro* (53,54,55), and they have been detected in the pancreata of type 1 diabetes patients (56). Animal studies suggest that the timing of an infection may be critical. The outcome of infection may differ in individuals with islet autoimmunity compared to those with unaffected islets. The outcome is also modulated by complex interactions between the microbe and the host, e.g., variants of the innate immune system receptor interferon-induced helicase C domain-containing protein 1 (IFIH1) may determine viral load (57). Despite a number of studies using different approaches, the nature of the relationship between enteroviruses and type 1 diabetes remains controversial. In most cases, diagnosis of type 1 diabetes follows a long period of preclinical islet autoimmunity. Viruses present at diagnosis may have infected the host late in the disease process rather than trigger the process. Alternatively, the triggering infection has likely been cleared by the time of diagnosis, unless the virus is able to persist. Enterovirus infections may potentially initiate islet autoimmunity, modulate progression to clinical type 1 diabetes (58,59,60,61,62), or both (Figure 11.2).

CASE-CONTROL STUDIES OF ENTEROVIRAL INFECTIONS AT THE DIAGNOSIS OF TYPE 1 DIABETES
Enterovirus Serology
The initial observation of an association between enteroviral infections and type 1 diabetes made by Gamble *et al.* in 1969 (63) was based on apparently higher prevalence of antibodies against Coxsackie virus in patients with recently diagnosed type 1 diabetes than in controls. Controls were poorly selected, older than the cases, thus less likely to have had a recent infection. That study did not adjust for likely differences in the HLA genotypes among cases and controls. The HLA genotypes associated with type 1 diabetes are a powerful confounder, as they are also associated with a more vigorous antibody response to infection than the other genotypes (64,65). However, none of the 13 studies published up to 2002 (66) determined HLA type in cases and controls. This has helped to reinforce the possibly false-positive initial finding by Gamble. The review by Green *et al.* (66) concluded that heterogeneity in assays, study design, and results did not allow a conclusion or calculation of a pooled estimate. Smaller studies included in that review had larger estimated odds ratios, suggestive of a publication bias (66). Separate analyses performed for antibodies specific for Coxsackie viruses B3, 4, and 5 (based on 11, 17, and 11 studies, respectively) revealed little or no association overall. Most of the limitations plaguing the early seroepidemiologic studies apply also to more recent studies using reverse transcription-polymerase chain reaction (RT-PCR) for enterovirus detection, covered in the next section.

Enterovirus RNA in Blood Samples
Yeung *et al.* reviewed studies using modern methods of enterovirus detection (67). This meta-analysis unfortunately pooled estimates across all studies despite the presence of significant heterogeneity in the study designs and results (68). For instance, methods of detection included *in situ* hybridization or immunohistochemistry on pancreatic tissue, as well as RT-PCR on blood samples.

A less heterogeneous re-analysis of RT-PCR studies utilizing serum, plasma, or whole blood among newly diagnosed type 1 diabetes patients and matched controls is presented in Figure 11.3 (52). The overall results were consistent with an odds ratio of approximately 10 (Figure 11.3A) (69,70,71,72,73,74,75,76) and
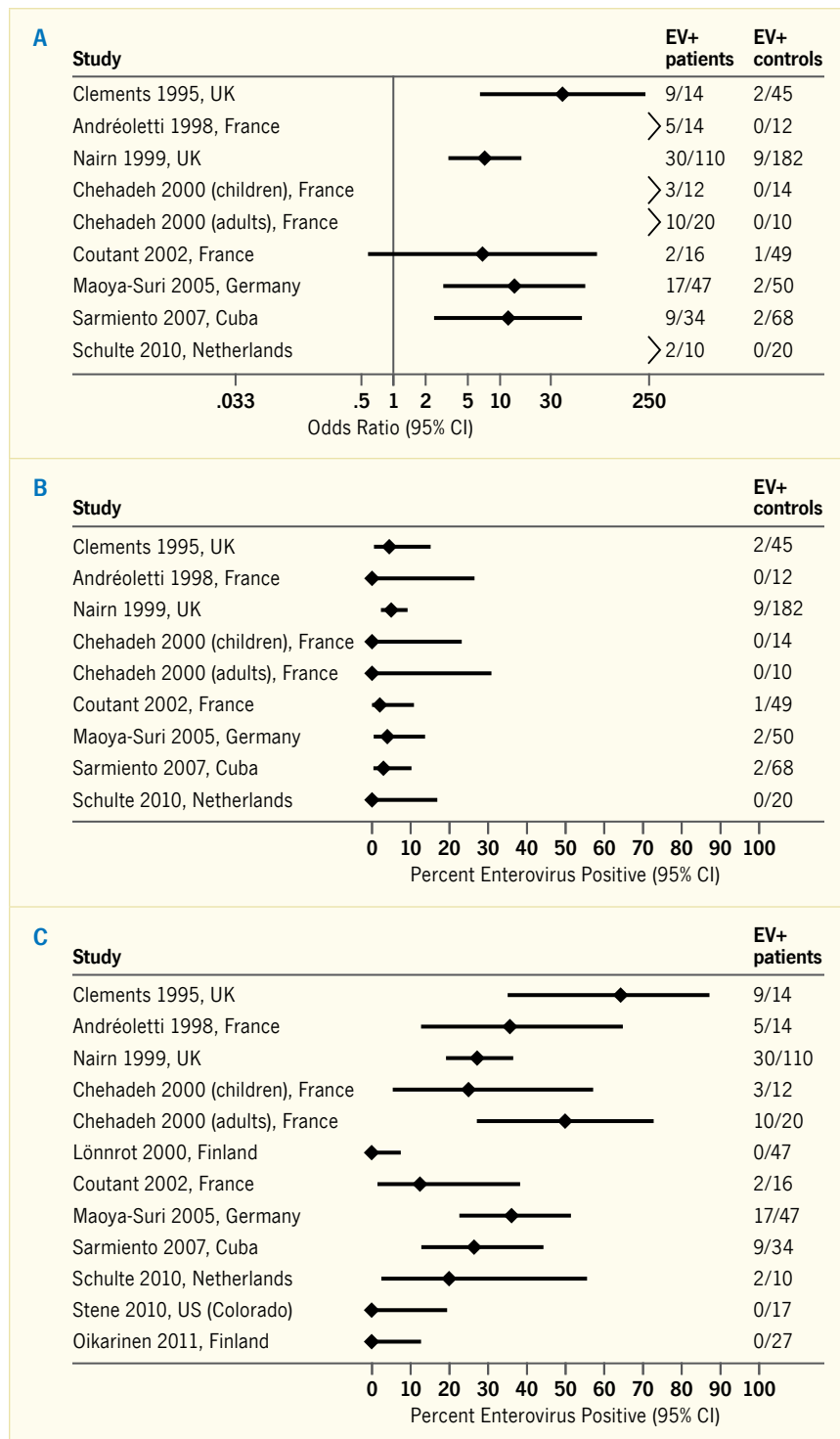
low heterogeneity among the studies (the I-square estimate was 0%). While the studies varied little in the frequency of enterovirus RNA in healthy controls (Figure 11.3B) (69,70,71,72,73,74,75,76), there was wide variation in the frequency of enterovirus RNA in newly diagnosed type 1 diabetes patients (Figure 11.3C) (62,69,70,71,72,73,74,75,76,77,78). The earliest studies showed a higher frequency of infection among patients than did the more recent ones. It is notable (Figure 11.3C) that one laboratory found no enterovirus RNA in any sample from type 1 diabetes patients at diagnosis in three independent data sets (62,77,78). This was the Finnish laboratory that has reported many positive samples from prediabetic individuals in longitudinal studies (62,78). Thus, lack of assay sensitivity would be unlikely. A large study reported a three times higher proportion of enterovirus RNA in serum from type 1 diabetes patients compared to controls, but interestingly, the majority of patients had longstanding diabetes (79).

PROSPECTIVE COHORT STUDIES OF ENTEROVIRUSES AND ISLET AUTOIMMUNITY
Prospective studies can exclude the possibility that the virus detected in patients infected them after disease onset. They can also demonstrate causation if a virus triggers autoimmunity through a "hit and run" mechanism. Challenges include sampling frequency to capture infectious agents while they are present in biological specimens and statistical power if the infection is rare or very common.

Does Enterovirus Trigger Islet Autoimmunity?
The longitudinal studies investigating enteroviral infections as potential triggers of islet autoimmunity are presented in Table 11.3 (15,62,64,77,78,80,81,82, 83,84,85,86,87, reviewed in 52). The largest studies include three Finnish projects: DIPP (Diabetes Prediction and Prevention Study), DiMe (Childhood Diabetes in Finland), and TRIGR (Trial to Reduce IDDM in the Genetically at Risk); the Colorado DAISY study (Diabetes Autoimmunity Study in the Young); the

FIGURE 11.3. Studies of Enterovirus RNA in Serum or Plasma From Patients With Type 1 Diabetes Diagnosed Within One Month and From Healthy Controls

A

Study		EV+ patients	EV+ controls
Clements 1995, UK		9/14	2/45
Andréoletti 1998, France		5/14	0/12
Nairn 1999, UK		30/110	9/182
Chehadeh 2000 (children), France		3/12	0/14
Chehadeh 2000 (adults), France		10/20	0/10
Coutant 2002, France		2/16	1/49
Maoya-Suri 2005, Germany		17/47	2/50
Sarmiento 2007, Cuba		9/34	2/68
Schulte 2010, Netherlands		2/10	0/20

.033 .5 1 2 5 10 30 250
Odds Ratio (95% CI)

B

Study		EV+ controls
Clements 1995, UK		2/45
Andréoletti 1998, France		0/12
Nairn 1999, UK		9/182
Chehadeh 2000 (children), France		0/14
Chehadeh 2000 (adults), France		0/10
Coutant 2002, France		1/49
Maoya-Suri 2005, Germany		2/50
Sarmiento 2007, Cuba		2/68
Schulte 2010, Netherlands		0/20

0 10 20 30 40 50 60 70 80 90 100
Percent Enterovirus Positive (95% CI)

C

Study		EV+ patients
Clements 1995, UK		9/14
Andréoletti 1998, France		5/14
Nairn 1999, UK		30/110
Chehadeh 2000 (children), France		3/12
Chehadeh 2000 (adults), France		10/20
Lönnrot 2000, Finland		0/47
Coutant 2002, France		2/16
Maoya-Suri 2005, Germany		17/47
Sarmiento 2007, Cuba		9/34
Schulte 2010, Netherlands		2/10
Stene 2010, US (Colorado)		0/17
Oikarinen 2011, Finland		0/27

0 10 20 30 40 50 60 70 80 90 100
Percent Enterovirus Positive (95% CI)

Note that three studies of patients with newly diagnosed type 1 diabetes did not include matched controls and are thus not included in panels A and B. (A) Odds ratio for association between enterovirus and type 1 diabetes estimated using Woolf's formula, as information for matched analysis was not provided in original publications. The I-squared estimate of statistical between-study heterogeneity was 0.0%. Odds ratio estimates cannot be calculated from studies with zero observed controls with enterovirus. Overall results (association and heterogeneity) were similar after adding 0.5 to all four cells in the 2x2 table for studies with zero observed controls with enterovirus RNA positive serum (data not shown). (B) Percent enterovirus-positive age-matched healthy controls (with exact 95% confidence intervals). (C) Percent enterovirus-positive type 1 diabetes patients. CI, confidence interval; EV, enterovirus.

SOURCE: Reference 52, copyright © 2012 John Wiley & Sons, reprinted with permission, and references cited (first author and publication year indicated in figure) are 62, 69, 70, 71, 72, 73, 74, 75, 76, 77, and 78. Data from Oikarinen 2011 (78) include data not presented in original publication, obtained by personal communication from H. Hyöty and S. Oikarinen, Tampere, Finland. Figure does not include data based on enterovirus detection in peripheral blood mononuclear cells, which are available from Schulte et al. (76).

Norwegian MIDIA (Environmental Triggers of Type 1 Diabetes); and the German BABYDIAB and BABYDIET studies. Preliminary data from a study in Australia called VIGR (Viral etiology of type 1 diabetes) have only been presented in abstract form, but the results were included in the meta-analysis by Yeung et al. (67) (Table 11.3). These studies followed children with increased risk of type 1 diabetes, defined by a first degree family history, HLA susceptibility genes, or both, with serial tests of serum or stools for evidence of enterovirus infections. These seven studies have published data from a total of 176 cases of islet autoimmunity; DiMe followed only children with islet autoimmunity for type 1 diabetes as the endpoint. Sample frequency and method of virus detection varied. Results of the prospective studies were reviewed by Stene and Rewers (52) and are summarized in Table 11.4 (64,67,80,83,84,85,86,87).

Presence of Enteroviral RNA in Stool. Three studies (DIPP, MIDIA, and BABYDIET) reported separate data from stool samples; none showed any significant association with islet autoimmunity (85,86,87). In MIDIA, the lack of association remained also when restricting to periods just prior to seroconversion, and there was also no difference when counting samples after seroconversion for islet autoantibodies (87). In DIPP, there was a tendency towards an association, but the result was only significant when combined with enterovirus serology (85). In the BABYDIET study, some infections may have been missed because of sampling every 3 months rather than monthly and only up to age 12 months, while most cases seroconverted to islet autoimmunity at a later age (mean 2.6 years, up to 7.9 years) (86).

Presence of Enteroviral RNA or Antibodies in Serum. DIPP and TRIGR reported significant associations with islet autoimmunity when combining enterovirus RNA in serum with infections defined serologically based on serial increase in at least one of several assays. The fact that the large majority of infections were detected

TABLE 11.3. Longitudinal Studies of Enterovirus and Islet Autoimmunity or Type 1 Diabetes

STUDY, YEARS (REF.)	POPULATION	AGE (MONTHS) AT SAMPLE COLLECTION	DEFINITION OF ISLET AUTOIMMUNITY; NUMBER OF CASES TESTED FOR ENTEROVIRUS	TYPE OF SAMPLE AND ENTEROVIRUS ASSAY
DiMe, 1986–1993 (77,81)	Siblings of newly diagnosed children with type 1 diabetes in Finland	6 month intervals from type 1 diabetes diagnosis in sibling	≥1 of ICA, IAA, GADA, IA2A; 11 cases	Serum, serology, and RT-PCR
DIPP, 1994–2003 (15,78,82,83,84,85)	Newborns with moderate- or high-risk HLA genes in Finland	Cord, (3), 6, (9), 12, (15), 18, (21), 24, (30), 36, … ( ) denotes samples in high-risk HLA subjects only	ICA (IAA, GADA, IA2A measured if ICA positive); up to 41 cases	Serum (plus fecal samples), serology, and RT-PCR
Second pilot of TRIGR, 1995–1999 (83)	Newborns with family history of type 1 diabetes in Finland	Cord, 3, 6, 9, 12, 18, 24	≥1 of IAA, GADA, IA2A, ICA; 19 cases	Serum, serology, and RT-PCR
BABYDIAB, 1989–1997 (80)	Offspring of patients with type 1 diabetes in Germany	Cord, 9, 24, 36, 60, 96	≥1 of IAA, GADA, IA2A, ICA; 28 cases	Serum, Coxsackie virus serology
DAISY, 1993–ongoing (64)	Relatives of type 1 diabetes and newborns with moderate- or high-risk HLA genes in Colorado	9, 12, 15, 24, then annually	≥1 of IAA, GADA, IA2A on ≥2 consecutive occasions; up to 26 cases	Serum, rectal swabs, saliva, RT-PCR
DAISY, 1993–ongoing (62)	As above	3–6 month intervals from islet autoimmunity	140 cases of islet autoimmunity tested, of which up to 50 progressed to type 1 diabetes	Serum, rectal swabs, RT-PCR (serology in subsample)
MIDIA, 2001–2006 (87)	Newborns with the high-risk HLA genes in Norway	Every month from ages 3 to 36 months	≥2 of IAA, GADA, IA2A on ≥2 consecutive occasions; 27 cases	Fecal samples, RT-PCR
BABYDIET, 2000–2006 (86)	Relatives of type 1 diabetes and newborns with moderate- or high-risk HLA genes in Germany	3, 6, 9, 12 months	≥1 of IAA, GADA, IA2A, Zn-T8A; 22 cases	Fecal samples, RT-PCR, cell culture
Systematic review through 2010 (67)	Newborns with family history of type 1 diabetes in Australia	Every 6 months from ages 6 to 30 months	≥2 of IAA, GADA, IA2A; 13 cases	Serum, RT-PCR

DAISY, Diabetes Autoimmunity Study in the Young; DiMe, Childhood Diabetes in Finland Study; DIPP, Diabetes Prediction and Prevention Study; GADA, glutamic acid decarboxylase autoantibodies; HLA, human leukocyte antigen; IA2A, insulinoma antigen 2 autoantibodies; IAA, insulin autoantibody; ICA, islet cell autoantibodies; MIDIA, Environmental Triggers of Type 1 Diabetes Study; RT-PCR, reverse transcription-polymerase chain reaction; TRIGR, Trial to Reduce IDDM in the Genetically at Risk; ZnT8A, zinc transporter 8 autoantibody.

SOURCE: References are listed within the table.

with serology suggests that serology was driving this association (82,84). Another DIPP report (88) found no significant association between serologically defined infections in serial samples from age 3–24 months and later risk of islet autoimmunity in 107 children with islet autoimmunity and 446 matched controls. BABYDIAB analyzed enterovirus serology (80), but infrequent sampling and, in many instances, only one or no sample available from before islet autoimmunity limited the power to detect any relationship. Graves *et al.* (64) in DAISY found no significant serologic association between enterovirus and islet autoimmunity (M. Rewers, unpublished observation). Notably, these longitudinal studies rarely, if ever, detected enterovirus RNA continuously in the same individual for more than about 3 months, thus providing no evidence for detectable persistent infection.

Does Enterovirus Influence Progression From Islet Autoimmunity to Type 1 Diabetes?

DiMe and DIPP have found that positive enterovirus RNA and serology preceded development of type 1 diabetes (77,78,81). The hypothesis that enterovirus infections can promote progression from islet autoimmunity to type 1 diabetes is consistent with animal model data (58,89). Among children with islet autoimmunity, DAISY was the first to report a higher rate of progression to type 1 diabetes in sample intervals after detection of enterovirus RNA in serum (62). Remarkably, none of the samples available from the day of type 1 diabetes diagnosis was positive for enterovirus RNA. This suggests that the observed association was not due to reverse causality.

PRENATAL ENTEROVIRUS INFECTION AND DEVELOPMENT OF TYPE 1 DIABETES

Some studies have suggested a relationship between prenatal infections and risk of type 1 diabetes in childhood (81,90,91,92), while a number of others have not found any significant relationship (80,83,84,93). There are many methodologic differences between these studies, including timing of exposure assessment (the first trimester, third trimester, or birth).

THE POLIO MODEL OF TYPE 1 DIABETES

The analogy between the epidemiology of poliomyelitis and that of type 1 diabetes was pointed out a long time ago (94). Poliovirus and enteroviruses belong to the same family of Picornaviridae. Prior to 1880, most infants were infected with poliovirus during the first year

TABLE 11.4. Postnatal Enterovirus Infections Before Islet Autoimmunity and the Corresponding Period for Matched Controls From Longitudinal Birth Cohort Studies

TYPE OF ENTEROVIRUS ASSAY/SAMPLE, STUDY, YEARS (REF.)	PER SAMPLE RESULTS EV+ Case Samples Versus EV+ Control Samples Odds Ratio (95% CI)	PER SUBJECT RESULTS Case Subjects EV+ at Least Once Versus Controls Odds Ratio (95% CI)
RNA in feces		
DIPP, 1994–1999 (85)	NR	5/12 (42%) vs. 15/53 (28%) OR 1.8 (0.5–6.6)
MIDIA, 2001–2006 (87)	43/339 (13%) vs. 94/692 (14%) OR 1.0 (0.6–1.7)	18/27 (67%) vs. 30/53 (57%) OR 1.5 (0.6–4.0)
BABYDIET, 2000–2006 (86)	5/72 (7%) vs. 27/267 (10%) OR 0.7 (0.2–2.2)	4/22 (18%) vs. 20/82 (24%) OR 0.7 (0.2–2.3)
RNA in serum		
DIPP, 1994–1999 (84)	NR	NR
TRIGR, 1995–1999 (83)	NR (14%) vs. NR (8.4%) OR 1.8 (NR)	NR
Systematic review through 2010 (67)	NR	5/13 (38%) vs. 28/198 (14%) OR 3.8 (1.2–12)
Serology		
BABYDIAB, 1989–1997 (80)	0/62 (0%) vs. NR	0/28 (0%) vs. NR
Combination of methods		
Serology and/or serum RNA; DIPP, 1994–1999 (84)	33/152 (22%) vs. 105/751 (14%) OR 1.7 (1.1–2.6)	NR
Serology and/or serum RNA; TRIGR, 1995–1999 (83)	NR (0.83 vs. 0.29 infections per child reported significantly different)	NR
RNA in rectal swab or saliva; DAISY (64)	0/17 (0%) vs. 3/35 (9%)	0/10 (0%) vs. 3/21 (14%)
EV RNA in serum, rectal swab, or saliva; DAISY (relatives) (1993–ongoing) (64)	1/10 (10%) vs. 2/8 (25%) OR 0.3 (0.02–4.6)	1/6 (17%) vs. 2/6 (33%) OR 0.4 (0.03–6.2)

CI, confidence interval; DAISY, Diabetes Autoimmunity Study in the Young; DiMe, Childhood Diabetes in Finland Study; DIPP, Diabetes Prediction and Prevention Study; MIDIA, Environmental Triggers of Type 1 Diabetes Study; NR, not reported; OR, odds ratio; RNA, ribonucleic acid; TRIGR, Trial to Reduce IDDM in the Genetically at Risk.

SOURCE: References are listed within the table.

of life (12). These infections were generally mild due to the presence of maternal anti-poliovirus antibodies transmitted transplacentally or in breast milk (95). Viremia was limited, and infection of the central nervous system and paralysis were rare. Importantly, infants acquired active immunity under the cover of passive protection. Improved hygiene led to a delay of the initial infections past the passive protection period. The median age at poliovirus infection increased gradually with associated morbidity until widespread vaccination became available.

It has been hypothesized that in countries with the highest incidence of type 1 diabetes, increased hygiene and sanitation resulted in a decline in herd immunity to enteroviruses among pregnant women, exposing fetuses and newborns to prenatal or infant enteroviral infections (96). While direct evidence for this in humans is lacking, virus-induced diabetes can be prevented in animal models of offspring by infecting mothers with the same virus prior to pregnancy (97). There are, however, important differences between the epidemiology of poliomyelitis and type 1 diabetes. In contrast to polio, the age at diagnosis of type 1 diabetes has been declining with the increase in incidence. It could potentially be explained by an increase in the proportion of type 1 diabetes caused by prenatal enteroviral infections resulting in viral persistence in the pancreas (56,98).

THE HYGIENE HYPOTHESIS AND POTENTIAL PROTECTIVE EFFECT OF NATURAL INFECTIONS

The hygiene hypothesis suggests that autoimmune diseases may be on the rise due to a decreasing frequency of child-hood infections from improved hygiene (99,100,101). Children living with siblings and sharing a bedroom have lower risk of type 1 diabetes (102). Infections in early life, routinely recorded by family doctors, have not been associated with subsequent childhood type 1 diabetes in a U.K. population-based study of 367 cases and 4,579 matched controls (103). There was no evidence of any reduction in the subsequent risk of diabetes in children with at least one infection in the first year of life (OR 1.03, 95% confidence interval [CI] 0.79–1.34) or in children prescribed antibiotics in the first year of life (OR 1.03, 95% CI 0.82–1.29). Analyses of infections in the first 2 years of life reached similar conclusions. However, prospective studies have reported a significant association between early childhood infections and islet autoimmunity. The BABYDIET study found respiratory infections during the first 6 months of life predictive of islet autoimmunity (hazard ratio [HR] 2.27, 95% CI 1.32–3.91); the association was weaker for infections between ages 6 and 12 months (HR 1.32, 95% CI 1.08–1.61) and absent beyond 1 year of age (104). Similar results were reported from Norway (105), while the DAISY study in Colorado found an association between islet autoimmunity and early childhood gastrointestinal infections, but not respiratory infections. In summary, prospective studies generally do not support the hygiene hypothesis for type 1 diabetes.

OTHER VIRUSES

Congenital rubella syndrome results in persistent viral infection followed by diabetes in about 20% of children (106,107). The onset of type 1 diabetes in these cases was delayed into the second or third decade of life, and >20% of those diagnosed did not require insulin (108). Most of those patients who developed diabetes did not have islet autoantibodies using early, poorly standardized assays (109,110). The mechanisms by which the

rubella virus may cause these diseases are not well characterized; however, molecular mimicry has been invoked (111,112). A review has highlighted gaps in the evidence linking congenital rubella infections with type 1 diabetes (113).

Rotavirus also infects beta cells (114) and may have a link to islet autoimmunity by way of molecular mimicry (115); however, evidence for a causal role is lacking (116). A longitudinal Australian study reported an increased incidence of islet autoantibodies shortly after detection of rotavirus infection (117). The limitation of this study was diagnosis of infection based on measurement of serum rotavirus antibodies rather than detection of viral presence in stool by PCR. A Finnish study that measured rotavirus antibodies in serum samples collected at 3–6-month intervals up to age 2 years did not confirm the association (118).

A causal link between mumps and type 1 diabetes has long been suggested. Mumps epidemics were sometimes followed by sudden, sharp increases in type 1 diabetes onset a few years later (119), and the presence of islet-specific antibodies correlated with mumps infections (120). However, despite near-eradication of mumps through routine childhood vaccination, type 1 diabetes incidence is still rising, suggesting that mumps is not a trigger of type 1 diabetes.

Cytomegalovirus (CMV) has also been implicated in the etiology of type 1 diabetes, primarily using serological evidence (121,122,123). In contrast, several epidemiologic studies have failed to demonstrate a link between CMV and the development of islet autoantibodies or type 1 diabetes (124,125,126). A more recent study analyzed specifically a possible association between perinatal CMV infection and islet autoantibodies in young children with type 1 diabetes risk-associated HLA genotypes and found none (127).

The Kilham rat virus (KRV), a member of the parvovirus family, is sufficient to induce type 1 diabetes in diabetes-resistant

BioBreeding (BB) rats that do not spontaneously develop diabetes (128). The incidence of human parvovirus infections peaks in childhood, the virus is endemic with irregular intervals of outbreaks, and it promotes a T cell-mediated lymphoproliferative response that could generate autoimmunity. Parvovirus has been related to type 1 diabetes, rheumatoid arthritis, and Grave's disease in small clinical case-control studies (129,130). A homology between the parvovirus B19 and the extracellular domain of IA-2 islet autoantigen suggests a potential mimicry (131). However, case-control studies have, so far, been negative (132).

Several additional viruses (133,134,135, 136) have been associated with onset of type 1 diabetes, but confirmation is lacking. In summary, it has not been established beyond reasonable doubt that any of the candidate infections triggers islet autoimmunity or accelerates islet autoimmunity toward diabetes in a large number of patients. Further prospective studies of these candidate triggers, as well as of other microbial agents, are therefore warranted in subjects at increased type 1 diabetes risk.

High-throughput ("next generation") sequencing technologies are being applied to human studies of viruses in causation of type 1 diabetes (137). With larger and higher quality data sets in the future, such as those expected from the TEDDY study (11), more sophisticated statistical analyses are being applied to separate information from noise. Progress in sequencing technologies has offered attractive new possibilities to detect microbes in biological samples and carry out metagenomic studies where the whole microbiome and virome can be explored in the context of islet autoimmunity and type 1 diabetes. This concerns not only all known microorganisms represented in GenBank (*www.ncbi.nlm.nih.gov/genbank/*), but also novel ones.

INTESTINAL MICROBIOTA

In addition to viruses, bacterial infections and commensal microbiota may modulate the risk of type 1 diabetes (138). The

mucosal immune system has specialized regulatory mechanisms to tolerate commensal microorganisms. Some of the candidate environmental factors that appear to affect the risk of type 1 diabetes (e.g., cesarean section delivery, early childhood diet, use of antibiotics) are intertwined with the development and function of the human microbiome. Intestinal bacteria have also been related to type 2 diabetes, inflammatory bowel diseases (139), rheumatoid arthritis (140), atherosclerosis, allergy, colon cancer, and a host of other diseases, but the effect appears to be nonspecific. There is growing evidence that the "Western" diet has altered the genetic composition and metabolic activity of the gut microbiota. Emerging data support the hypothesis that altered gut bacterial composition may play a role in development of type 1 diabetes (141,142,143,144,145,146,147). Gut microbes influence lipid and glucose metabolism, as well as immunity and systemic inflammation outside of the intestine (141,148,149,150); therefore, they could be considered as a target in prevention of metabolic and proinflammatory diseases. In general, however, microbiome studies in the context of type 1 diabetes have, thus far, been underpowered and focused on taxa diversity. Some have reported lower microbial diversity in children with islet autoimmunity before progression to diabetes compared to healthy controls (138,142,147). The picture remains unclear at this time and will require large studies that employ whole genome sequencing of microbiome at multiple time points prior to diagnosis.

VACCINES

As childhood immunization programs have expanded, there has been speculation that vaccines may play a role in the development of childhood diseases that have risen in incidence, such as type 1 diabetes (151). Fortunately, no association between immunizations and islet autoimmunity or type 1 diabetes has been found thus far (14,152,153,154). A meta-analysis reviewed 23 studies investigating 16 vaccinations and analyzed 11 studies that met the inclusion criteria (155). Overall, there was no evidence to

suggest an association between any of the childhood vaccinations investigated and type 1 diabetes. The pooled odds ratios ranged from 0.58 (95% CI 0.24–1.40) for the measles, mumps, and rubella (MMR) vaccination in five studies up to 1.04 (95% CI 0.94–1.14) for the haemophilus influenza B (HiB) vaccination in 11 studies. Significant heterogeneity was present in most of the pooled analyses but was markedly reduced when analyses were restricted to study reports with high methodology quality scores.

The Bacillus Calmette-Guérin (BCG) vaccine has attracted some interest as a potential immunomodulator that could theoretically reduce the incidence of autoimmune diabetes. However, human data for any association between BCG vaccination and type 1 diabetes or islet autoimmunity are universally negative. Until recently, BCG has been routinely administered to all neonates in Finland, the country with the highest incidence of type 1 diabetes worldwide. Case-control studies from Canada (156) and Sweden

(157) have shown no association of BCG vaccination with the risk of diabetes. Likewise, the German BABYDIAB study (158) reported no association with development of islet autoimmunity. A 20-year follow-up of the 1974 Canadian birth cohort, of which 45% were given BCG in the first year of life, also showed no association (159). In addition, vaccination with BCG at diagnosis of type 1 diabetes does not increase the remission rate or preserve beta cell function (160,161).

DIETARY FACTORS

Dietary factors associated with the appearance of islet autoimmunity and progression from islet autoimmunity to type 1 diabetes are reviewed in this section.

BREASTFEEDING

An ecologic study suggested an association between the decrease in breastfeeding and increase in type 1 diabetes incidence between 1940 and 1980 (162). Subsequent case-control studies have been inconsistent regarding whether breastfeeding was associated with a decreased risk of type 1 diabetes, as reviewed by Knip *et al.* (163), and two meta-analyses reached opposite conclusions (164,165). In 2012, a pooled analysis was conducted of 43 retrospective studies, showing a small reduction in the risk of type 1 diabetes associated with exclusive breastfeeding for >3 months (OR 0.87, 95% CI 0.75–1.00) and any (i.e., nonexclusive) breastfeeding for >3 months (OR 0.88, 95% CI 0.78–1.00) (166). The authors concluded that the findings were difficult to interpret because of the possible biases (particularly recall bias) inherent in the included studies.

All but one of the prospective cohort studies failed to find an association between breastfeeding duration and islet autoimmunity (14,167,168,169,170, 171,172,173). In Sweden, breastfeeding <4 months was associated with the presence of islet autoantibodies at age 5 years (OR 2.09, 95% CI 1.45–3.02) compared to breastfeeding for ≥4 months (174). DAISY found evidence that a child

who is still breastfeeding at the time of introduction to cereals has a reduced risk of islet autoimmunity (168), and a subsequent analysis in DAISY showed that breastfeeding at the time of introduction to gluten-containing grains, specifically, conferred protection for the development of type 1 diabetes (HR 0.47, 95% CI 0.26–0.86) (169). A similar protective relationship between breastfeeding and the introduction of gluten has been observed in celiac disease (175). These findings suggest that while not strongly protective independently, breastfeeding may be a protective factor in the relationship between other dietary factors, including but not limited to cereals and gluten, and type 1 diabetes (as further described in the following sections).

MATERNAL DIET

Reports attempting to examine the association between maternal diet and islet autoimmunity have not produced supporting evidence. Investigators from Sweden found that a low consumption of vegetables (<1 time/week) in the maternal diet was associated with a *higher* risk of islet autoimmunity in the child (OR 2.89, 95% CI 1.18–7.05) (176). In the United States, a lower consumption of potatoes by mothers during pregnancy was associated with a *higher* risk of islet autoimmunity in the child (177).

COW'S MILK

Breastfeeding may be viewed as a surrogate for the delay in the introduction of diabetogenic substances, such as

cow's milk, that are present in formula. Cow's milk introduced at weaning has been shown to trigger insulitis and diabetes in animal models (178,179). Numerous studies have been conducted examining the association between age at introduction of cow's milk and type 1 diabetes or islet autoimmunity, as reviewed in Knip *et al.* (163), and they have been inconsistent. One meta-analysis of case-control studies (165) and a nested case-control study of a cohort study (180) suggest an increased risk; a second meta-analysis (164) and all of the prospective cohort studies failed to show any association between age at introduction of cow's milk and either islet autoimmunity (168,170,171,172,173,181) or type 1 diabetes (169).

In a double-blind, randomized trial in Finland (TRIGR Pilot), 230 infants at genetically increased risk for type 1 diabetes were assigned to receive either a casein hydrolysate formula or a conventional, cow's milk-based formula (control) whenever breast milk was not available during the first 6–8 months of life (182). The incidence of islet antibodies was significantly lower in children fed the casein hydrolysate formula in comparison to the group with conventional cow's milk-based formula (HR 0.54, 95% CI 0.29–0.95) (182). A larger, multinational randomized intervention study of this same hypothesis, TRIGR, has found no effect on development of islet autoimmunity (183); follow-up of the study participants for type 1 diabetes is underway.

Studies exploring the role of current, i.e., childhood, cow's milk consumption in the risk for islet autoimmunity and type 1 diabetes have also produced contradictory results. Cow's milk intake in childhood has been associated with both an increased risk of islet autoimmunity (184,185,186) and type 1 diabetes (187,188), as well as a decreased risk of type 1 diabetes (189). A Finnish study found that cow's milk consumption during childhood was more closely linked to islet autoimmunity and type 1 diabetes risk than was infant (early) exposure to cow's milk (188). A nested case-control study within the Finnish DIPP cohort found that increased cow's milk intake during childhood was weakly associated with increased islet autoimmunity risk (184). While a similar analysis in the DAISY cohort found no association between cow's milk intake and islet autoimmunity risk, increased cow's milk intake was associated with progression to type 1 diabetes in children with islet autoimmunity (HR 1.59, 95% CI 1.13–2.25) (190). In DIPP (191), investigators evaluated whether serum fatty acids differed between children developing islet autoimmunity and those remaining autoantibody negative. Myristic acid, pentadecanoic acid, monounsaturated palmitoleic acid isomers 16:1 n-7 and 16:1 n-9, and conjugated linoleic acid were positively associated with the risk of islet autoimmunity at or before the time of seroconversion. Because these serum fatty acids are biomarkers of milk and ruminant meat fat (192,193), this suggests that higher current consumption of milk and meat may be associated with risk of islet autoimmunity. The inconsistencies across these studies may be due to the modifying effects of the underlying genetic profile. This is further described in the *Gene X Environment Interactions* section.

The reports that newly diagnosed diabetic children compared with age-matched controls have higher levels of serum antibodies against cow's milk proteins (194,195) have been difficult to reproduce (196). Prospective studies have also been contradictory: the Finnish TRIGR Pilot study showed higher levels of cow's milk antibodies in infancy prior to the development of type 1 diabetes (197), whereas DAISY did not observe elevations of the cow's milk IgG4 antibody, beta-lactoglobulin, prior to islet autoimmunity or type 1 diabetes (198).

SOLID FOODS AND CEREALS

In addition to breast milk substitutes, such as infant formulas, the infant is exposed to other dietary antigens in the first year of life that may impact oral tolerance or the immune system. Prospective studies of children at increased risk for type 1 diabetes from both Germany (BABYDIAB) and Colorado (DAISY) have shown an increased risk for islet autoimmunity associated with first exposure to cereals prior to the third month of life when compared with introduction in the fourth to sixth months of life. In DAISY, the timing of introduction of any type of cereal (gluten and non-gluten-containing) was associated with an increased islet autoimmunity risk, and the study also found that there appears to be a U-shaped relationship between risk and age at introduction, the nadir of the curve occurring with introduction in the fourth to sixth months of life (168). In contrast, BABYDIAB showed the association with gluten specifically and found that a further protective effect was conferred if foods containing gluten were introduced after the sixth month (171). Given the difference in the defined dietary variables (the non-gluten-containing food variable in BABYDIAB contained non-cereal foods), it is difficult to determine whether the two studies actually contradict each other regarding whether the driving antigen was gluten. The Finnish prospective study (DIPP) suggested that introducing gluten-containing cereals between ages 5 and 5.5 months (the middle tertile of exposure) was associated with an increased risk of islet autoimmunity compared with introducing gluten after age 5.5 months (the third tertile of exposure), but only during the first 3 years of life (173). There was no increased risk of islet autoimmunity associated with introducing gluten earlier than age 5 months (the first tertile of exposure) compared with after age 5.5 months.

Because gluten is the environmental trigger for celiac disease, another childhood autoimmune disease with many similarities to type 1 diabetes, and because gluten is a component of many cereals, gluten has been extensively studied in the context of type 1 diabetes as a potentially important environmental exposure. In the BB diabetes-prone rat, gluten precipitates the onset of islet autoimmunity (199), and MacFarlane *et al.* identified a wheat storage protein called Glb1 that may be associated with islet damage, by observing that antibodies to this protein were detectable in patients with diabetes, but not in nondiabetic individuals (200). Intervention studies in islet autoantibody-positive children indicate that while a gluten-free diet may not decrease autoantibody titers (201,202), it may improve beta cell function (202). However, an intervention study, in which 150 high-risk infants were randomly assigned to a first gluten exposure at age 6 months (control group) or 12 months (late-exposure group), found that delaying gluten exposure until age 12 months did not substantially reduce the risk for islet autoimmunity in genetically at-risk children, nor did it increase the risk (104,203).

Other solid foods in the infant diet, besides gluten and cereals, have been implicated in the etiology of islet autoimmunity. In Finland, DIPP found that introduction of root vegetables by age 4 months was associated with an almost twofold increased risk for islet autoimmunity compared with introducing root vegetables after age 4 months (173). They also found that first exposure to egg before age 8 months (the first tertile of exposure) was associated with an increased risk of islet autoimmunity compared with introducing egg after age 11 months (the third tertile of exposure), but only during the first 3 years of life (173). These cross-study differences may be related to country differences in the first solid food that is typically introduced to infants. In the United States, cereals, particularly rice cereal, are often the first solid foods to be introduced to the infant (168), whereas in other countries, root

vegetables and fruits are more common first solid foods, suggesting that the focus on cereals may not be relevant across countries and may explain these inconsistent results.

More recently, DAISY and BABYDIAB have prospectively examined the relation of some of these dietary exposures to clinical diabetes in a cohort of children at increased risk for type 1 diabetes. In DAISY (169), both early (age <4 months) and late (age ≥6 months) first exposure to any solid food (compared with exposure at age 4–5 months) predicted development of type 1 diabetes (HR 1.91, 95% CI 1.04–3.51, and HR 3.02, 95% CI 1.26–7.24, respectively). Specifically, early exposure to fruit and late exposure to rice/oat predicted type 1 diabetes (HR 2.23, 95% CI 1.14–4.39, and HR 2.88, 95% CI 1.36–6.11, respectively). BABYDIAB (204) reported that exposure to gluten-containing foods before age 3 months, which occurred rarely, increased the risk of developing islet autoantibodies and type 1 diabetes (n=3) compared to exclusive breastfeeding (HR 3.45, 95% CI 1.04–11.48) or compared to first exposure to gluten between 3.1 and 6.0 months of age. In contrast to DAISY, children who received gluten-containing foods after age 6 months did not have an increased risk of islet autoantibodies, multiple islet autoantibodies, or type 1 diabetes.

These data suggest that there are specific times in infancy wherein exposure is associated with an increased risk of developing islet autoimmunity and type 1 diabetes. In aggregate, these studies lend support to the idea that general antigenic stimulation is more important than the actual antigen in this disease process. The risk associated with early exposure may suggest a mechanism involving an aberrant immune response to dietary antigens in an immature gut immune system among susceptible individuals. The increased risk predicted by late exposure to solid foods may be related to the larger amounts given at initial exposure to older children (168,175), nutrient deficiencies (205), and/or the cessation of breastfeeding before solid foods are introduced, resulting in a loss of the protective effect of breast

milk at the introduction of foreign food antigens (168,169,175), described earlier in this chapter.

VITAMIN D

Vitamin D has been examined as a potentially protective factor, because it plays an active role in the regulation of the immune system, as well as metabolic pathways relevant to diabetes. Mechanistically, vitamin D has been shown to shift the balance of the body's T cell response toward down-regulation of the Th1 immune response (206). Both *in vitro* studies and animal studies have found that vitamin D stimulates a Th2 response (207,208,209). The Th1 response plays a key role in response to intracellular pathogens, primarily viruses and malignancies; its overactivation against autoantigens is thought to cause autoimmunity leading to type 1 diabetes. The Th2 response upregulates antibody production to fight extracellular organisms and promotes tolerance of the fetus during pregnancy; Th2 overactivation may lead to atopic dermatitis or asthma.

Vitamin D status during the intrauterine period may be of special importance for the development of the fetus (210). The seasonality of birth in children with type 1 diabetes and/or the presence of a seasonal pattern at diagnosis of type 1 diabetes could be explained by seasonal variation in endogenous vitamin D production via exposure to the sun (211,212). The monthly averages of maximal daily temperature and daily hours of sunshine were inversely related to the number of new patients per month in Belgium (213). Ecologic studies suggest that ultraviolet radiation exposure, which increases the body's ability to make vitamin D, is inversely associated with incidence of type 1 diabetes (214,215). However, epidemiologic studies of *in utero* vitamin D exposures have been inconsistent. In Finland, DIPP (216) examined the maternal diet during pregnancy and found that vitamin D intake was not associated with risk of islet autoimmunity nor type 1 diabetes in the child, which contradicts previous studies from the United States and Sweden that

found that maternal vitamin D intake during pregnancy was associated with a decreased risk of islet autoimmunity in the child (217,218). In a meta-analysis, the pooled odds ratio with maternal intake of vitamin D during pregnancy was 0.95 (95% CI 0.66–1.36), suggesting no effect of vitamin D intake (219). A Norwegian study found an association between higher serum 25-hydroxyvitamin D (25(OH)D) in samples collected in late pregnancy and lower risk of type 1 diabetes in the offspring (220), whereas a Finnish study found no such association with samples collected in the first trimester of pregnancy (221).

Multiple studies have examined the role of vitamin D exposure in infancy in the pathogenesis of type 1 diabetes. The EURODIAB multicenter case-control study found that diabetic children were less likely to have been given vitamin D supplements in infancy than control children (222). This finding is similar to that found in the previously described case-control study from Norway, where diabetic children were less likely to have been given cod liver oil supplements during infancy compared to controls (223). However, as fish oils contain both omega-3 fatty acids and vitamin D, it is not possible to attribute this association to one specific component. In a large, historical prospective study from Finland, infants who received no vitamin D supplementation had higher risk of type 1 diabetes than those who did receive supplements (224). Two meta-analyses of retrospective studies showed that the risk of type 1 diabetes was significantly reduced in infants who were supplemented with vitamin D compared to those who were not supplemented (pooled OR 0.71) (219,225). However, in a Swedish prospective study, no association was found between an intermediate dose of vitamin D supplementation during infancy and development of diabetes-related autoantibodies (218).

Determinants of circulating 25(OH)D, the inactive circulating form of vitamin D and an established marker of vitamin D status, include sun exposure, dietary intake

(supplements, fatty fish, and vitamin D fortified dairy foods), and genetic predisposition. The aforementioned studies were limited in that they were only able to examine vitamin D from supplements and were not able to examine vitamin D exposure either from foods or via sun exposure. DAISY examined the putative protective factor, vitamin D, and was the first large prospective study to show plasma 25(OH)D levels in infancy or throughout childhood were not associated with islet autoimmunity or progression from islet autoimmunity to type 1 diabetes in children at increased risk for type 1 diabetes (226). Dietary intake of vitamin D (from food and supplements) was also not associated with islet autoimmunity or progression to type 1 diabetes in the DAISY population (226). Interestingly, in a nested case-control study among non-Hispanic white U.S. active duty military personnel, those with 25(OH)D levels ≥100 nmol/L in blood samples measured prior to diagnosis had a 44% lower risk of developing type 1 diabetes than those with 25(OH)D levels <75 nmol/L (rate ratio 0.56, 95% CI 0.35–0.90) (227), suggesting a protective effect of vitamin D levels in adult-onset type 1 diabetes cases. While misclassification of type 1 and type 2 diabetes is common in young adults, results were similar in all study participants and those confirmed to have islet autoantibodies. Two clinical trials reported no effect of 1,25-dihydroxyvitamin D3 (calcitriol) supplementation on sustained insulin production among persons with new-onset type 1 diabetes (228,229). These inconsistent findings suggest that the mechanism by which vitamin D exerts its effect on type 1 diabetes is complex.

One missing component to the aforementioned analyses is the underlying genetic risk. Two GWAS identified variants located within or near genes involved in vitamin D transport (*DBP*), cholesterol synthesis (*DHCR7*), and hydroxylation (*CYP2R1* and *CYP24A1*) associated with 25(OH)D levels or vitamin D insufficiency (230,231). Genetic variants influencing 25(OH)D metabolism have been examined in association with both circulating 25(OH)D levels and type 1 diabetes (230,231,232).

FIGURE 11.4. Risk of Developing Islet Autoimmunity for Reported Dietary Intake of Omega-3 Fatty Acids and Omega-3 Fatty Acid Levels in Erythrocyte Membranes, Diabetes Autoimmunity Study in the Young (DAISY), 1994–2006
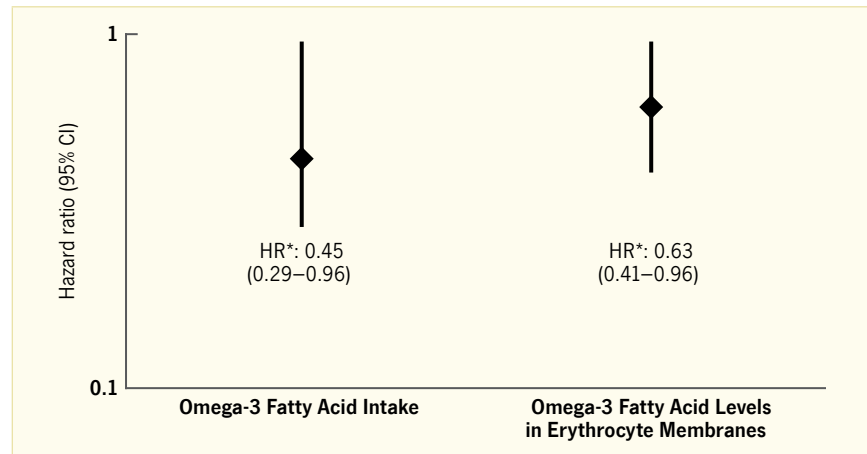
CI, confidence interval; HR, hazard ratio.
*   Hazard ratios calculated for 1-standard deviation difference in omega-3 levels, adjusted for human leukocyte antigen (HLA) genotype, family history of type 1 diabetes, and caloric intake (for intake variable only).
SOURCE: Reference 13

The associations found in the aforementioned GWAS were replicated (231) for four vitamin D metabolism genes (*DBP, DHCR7, CYP2R1,* and *CYP24A1*) with 25(OH)D in control subjects. *CYP27B1, DHCR7,* and *CYP2R1* were also associated with type 1 diabetes. *CYP27B1* had previously been associated with type 1 diabetes in 2007 (233). DAISY found that variants in *DHCR7* and *CYP27B1* were associated with development of islet autoimmunity, but not progression to type 1 diabetes, in children with islet autoimmunity (234). The *DHCR7* variant was also found to be associated with 25(OH)D levels in DAISY children; however, since 25(OH)D levels were not associated with islet autoimmunity or type 1 diabetes risk (226), the effect of this variant is not likely mediated through 25(OH)D levels, suggesting that this enzyme may influence diabetes risk via other mechanisms.

POLYUNSATURATED FATTY ACIDS
Several studies have demonstrated a strong effect of long-chain polyunsaturated fatty acids, specifically omega-3 fatty acids, on inflammatory responses in animals and humans (235,236). A relative deficiency of omega-3 fatty acids, a characteristic of many Western diets, may predispose to heightened inflammatory reactions and, thus, increase the risk for autoimmune diseases, such as type 1

diabetes. Alpha-linolenic acid (ALA) is the principal omega-3 fatty acid in Western diets and is found in the green leaves of plants and in flax, canola, walnuts, and soy. The next most common omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are found in fatty fish. Fatty acid levels in plasma or serum and fatty acid content of erythrocyte membranes are short-term and long-term markers of fatty acid status, respectively.

In Norway, a prospective study of DHA and EPA and other fatty acids in the phospholipid fraction of maternal serum collected in late pregnancy found no association with risk of type 1 diabetes before age 15 years (237). However, as mentioned previously, children with type 1 diabetes were less likely to have received cod liver oil (which contains DHA and EPA, along with vitamin D) in infancy (223) and had a decreased percentage of DHA in erythrocyte membranes (238) compared with controls. DAISY reported that higher omega-3 fatty acid intake during childhood was associated with a lower risk of islet autoimmunity and, likewise, that higher omega-3 fatty acid levels in the erythrocyte membrane were associated with a lower risk of islet autoimmunity (Figure 11.4) (13). In DIPP, while investigators did not find an association

between serum EPA or DHA and risk of islet autoimmunity, they showed that lower serum linoleic acid, an omega-6 fatty acid, was associated with increased risk of islet autoimmunity (191).

VITAMIN E

Animal models suggest that vitamin E, or α-tocopherol, may protect against diabetes (239,240). High maternal intake of vitamin E and other nutrients, such as retinol, beta-carotene, vitamin C, selenium, or manganese, was not associated with development of islet autoimmunity in children (241). Serum α-tocopherol, but not retinol or selenium, was inversely associated with type 1 diabetes in a small case-control study nested within a 21-year follow-up of adult Finnish men (242). In a cohort of initially nondiabetic siblings of children with type 1 diabetes, an inverse association with borderline significance between serum α-tocopherol concentrations and the risk of diabetes was observed (243). However, in DIPP, serum α-tocopherol concentrations were not significantly associated with the risk of islet autoimmunity (244).

ZINC

Studies have shown that serum, plasma, or intracellular zinc levels are significantly lower in type 1 diabetes patients than in controls (245,246). The role of zinc deficiency in triggering onset or progression of islet autoimmunity is unclear, but it could be related to the synthesis, storage, and secretion of insulin that require zinc for conformational integrity of insulin as a hexamer. Autoantibodies to ZnT8 are present in 60%–80% of newly diagnosed patients with type 1 diabetes (247). Ecologic studies suggest that the incidence rate of childhood diabetes is significantly higher in areas with lower levels of zinc in the drinking water (248,249). In Sweden, water samples from families with children with diabetes had lower concentrations of zinc (OR 0.72, 95% CI 0.57–0.90) than water samples from control families (250). A study from Finland suggests no association between maternal consumption of zinc during pregnancy and risk of islet autoimmunity (241).

WEIGHT GAIN, INSULIN RESISTANCE, AND BETA CELL STRESS

A number of studies have investigated the hypothesized association between obesity, insulin resistance, beta cell stress, and the development of type 1 diabetes (251,252) and have been reviewed by Rewers (253).

Birth Weight and Infant Growth

A study from Norway found an almost linear correlation between the incidence of type 1 diabetes and birth weight (254). The risk of type 1 diabetes was higher by more than twofold in children with birth weight >4,500 g in comparison to newborns with the lowest birth weight (<2,000 g) (254). Two meta-analyses suggest that children who are heavier at birth have a significant and consistent, but relatively small, increase in risk of type 1 diabetes (255,256). In addition, studies indicate that rapid weight gain during the first year of life is a risk factor for type 1 diabetes (257,258,259). These findings were confirmed in a meta-analysis (255). Another study showed that children developing diabetes had increased height gain at age 0–18 months and were significantly taller from ages 6 to 18 months compared with controls (260). However, DAISY showed that weight growth was not associated with risk of type 1 diabetes neither in the first 9 months nor in the first 15 months of life (height growth not measured before the age of 24 months) (169).

Height, Weight, and Body Mass Index

The "Accelerator Hypothesis" proposes that excess weight gain leading to increases in insulin resistance in early childhood initiates the autoimmunity leading to beta cell destruction and type 1 diabetes development (251). The rising blood glucose (glucotoxicity) may accelerate beta cell apoptosis directly or by inducing beta cell immunogens in genetically predisposed subjects. Ecologic studies have suggested a correlation between increasing body mass index (BMI), weight, and height, and incidence of type 1 diabetes in the population (261,262). Several studies have shown an association between higher BMI Z-scores and earlier age at diagnosis

of type 1 diabetes (263,264,265,266), although others have not (267,268,269). In case-control studies, children with type 1 diabetes showed increased weight, height, or BMI Z-scores in early childhood compared with nondiabetic children (260,270,271,272,273,274,275). Analysis of the 1970 British Birth Cohort suggested that increased BMI in childhood increased risk of self-reported type 1 diabetes (276). Similarly, in the Australian BabyDiab cohort, higher weight and BMI Z-scores were associated with development of islet autoimmunity (277). However, analyses of the prepubertal DAISY cohort showed that BMI was not associated with development of islet autoimmunity nor progression to type 1 diabetes and that height and weight were weakly *inversely* associated with risk of islet autoimmunity (278), which is contrary to the Accelerator Hypothesis. However, greater height growth *velocity* was associated with islet autoimmunity development and type 1 diabetes development, suggesting that velocity of growth and its related stressors may be involved in the progression from genetic susceptibility to islet autoimmunity and then to type 1 diabetes in prepubertal children. BABYDIAB participants positive for islet autoantibodies did not have an increased homeostasis model assessment of insulin resistance (HOMA-IR) compared with age-matched islet autoantibody-negative children at ages 8 or 11 years (279). Contrary to the accelerator hypothesis, islet autoimmunity status was associated with decreased HOMA-IR values, controlling for age and sex (p=0.01). BMI was similar between islet autoantibody-positive and autoantibody-negative children at ages 2, 5, 8, and 11 years and similar to that of national reference values (279).

In summary, small and inconsistent effects of height or weight have been reported by some studies, mostly from Scandinavia. These are likely not causally related to the autoimmune disease process in a vast majority of the cases.

Glycemic Index

In addition to growth, obesity, and insulin resistance, dietary factors, such as glycemic index and glycemic load, may also stress the beta cells. While *development of islet autoimmunity* was not associated with either, *progression to type 1 diabetes* in children with islet autoimmunity was associated with higher glycemic index and load at the first islet autoimmunity-positive visit (280), perhaps due to increased demand on the beta cells to release insulin.

TOXINS AND CHEMICAL COMPOUNDS

Toxins found in foods or water may activate autoimmune mechanisms in genetically susceptible individuals, and exposure to toxins may result in pancreatic islet cell death. Streptozotocin (281,282) or dietary nitrates and nitrosamines (283) induce islet autoimmunity in animal models. Circumstantial and ecologic evidence suggests a connection between type 1 diabetes and water containing nitrates, nitrites, or nitrosamines, although other studies have shown either no or contradictory associations (248,284,285). In a case-control study in Sweden, type 1 diabetes was associated with consuming higher amounts of foods containing nitrosamines (OR 1.7 and OR 2.6) and nitrates or nitrites (OR 0.8 and OR 2.4 for medium and high, respectively, compared with low amounts) (286). In Sweden, water samples from families with children with diabetes had higher concentrations of nitrate (OR 1.32, 95% CI 1.06–1.64) than water samples from control families (250). In Canada, only a nonsignificant trend between increasing consumption of nitrates in food and type 1 diabetes was observed (287). In Germany, water concentrations of nitrate and nitrite were not associated with risk of either islet autoimmunity or progression to type 1 diabetes progression (288).

Animal studies show that ingestion of subtoxic levels of bafilomycin, a natural toxin found in skins of *Streptomyces*-infected root vegetables, such as potatoes, by pregnant nonobese diabetic mice results in higher incidence and earlier onset of diabetes in their offspring (289,290,291). Thus, exposure to small quantities of bafilomycin in the maternal diet during pregnancy may contribute to risk of type 1 diabetes in the child.

METABOLOMIC STUDIES

The serum/plasma metabolite profile detected by combining gas and liquid chromatography followed by mass spectrometry has established metabolomics as a readout of phenotypes that has enabled the discovery of previously undetected associations between metabolic pathways and diseases. Metabolomics is central to the analysis of samples obtained prior to development of islet autoimmunity. These analyses can be used to test the hypothesis that a trigger(s) of islet autoimmunity induces or acts upon metabolic disturbances that predict the appearance of islet autoantibodies. Similarly, children with islet autoimmunity may express specific serum metabolite profiles heralding clinical onset of diabetes.

High genetic risk Finnish children followed since birth until diagnosis of type 1 diabetes had reduced serum levels of succinic acid and phosphatidylcholine already at birth. Furthermore, levels of lysophosphatidylcholine increased months before seroconversion to islet autoantibodies but normalized after seroconversion (292). An independent population of offspring of type 1 diabetes parents has suggested that higher levels of odd-chain triglycerides and polyunsaturated fatty acid-containing phospholipids may predict islet autoimmunity (293). In addition, children developing islet autoimmunity before age 2 years had lower levels of methionine than those developing islet autoimmunity at older ages (293).

A Swedish cohort study used umbilical cord blood lipidomic analysis to identify possible risk markers for the early development of type 1 diabetes while controlling for HLA genotype, sex, and date of birth, as well as mother's age and gestational age (294). A total of 106 lipid metabolites from cord blood samples were identified and, using principal component analysis, were analyzed for their predictive ability. In the children developing type 1 diabetes before age 4 years, lower levels of cord blood phospholipids (phosphatidylcholines, phosphatidylethanolamines, and sphingomyelins) all predicted development of type 1 diabetes, while in the children developing type 1 diabetes before age 2 years, triglycerides predicted type 1 diabetes. These results were replicated in a study of cord blood from children in the DIPP study, which also showed higher risk of progression to type 1 diabetes associated with lower levels of choline-containing phospholipids, including sphingomyelins and phosphatidylcholines (295).

The metabolomic studies to date present several leads for a search for the environmental factors that trigger islet autoimmunity and are involved in the increasing incidence of type 1 diabetes. The alterations in cord blood lipoprotein profiles noted in both the DIPP and Diabetes Prediction in Skåne (DiPiS) studies suggest that the intrauterine environment may affect type 1 diabetes risk. Further, the other early metabolomic changes may reflect specific alterations in the infant's microbiome. Other lipidomic and metabolomic changes noted above that precede the development of autoimmunity may reflect the activation of proinflammatory and anti-inflammatory mechanisms in early islet autoimmunity. While fascinating, these findings have to be interpreted with caution as the studies to date have been very small and remain to be replicated (for a comprehensive review see Frohnert and Rewers [296]).

PSYCHOSOCIAL AND SOCIOECONOMIC FACTORS

PSYCHOLOGICAL STRESS

A role of psychological stress in the etiology of type 1 diabetes has been suggested by case reports and small case-control studies (297). A cross-sectional study of 4,400 general-population children in Sweden found an association between presence of GAD autoantibodies at age 1 year and the history of high parenting stress (OR 1.8, 95% CI 1.2–2.9, p<0.01), serious life events (OR 2.3, 95% CI 1.3–4.0), foreign origin of the mother (OR 2.1, 95% CI 1.3–3.3), and low paternal education (OR 1.6, 95% CI 1.1–2.3), independent of family history of diabetes (298). The same group of investigators reported that mothers' experiences of divorce (OR 3.6, 95% CI 1.4–9.6) or violence (OR 2.9, 95% CI 1.0–7.8) were associated with islet autoimmunity in the children age 2.5 years (299). Finally, in a Danish cohort of 1,548,746 children, 39,857 children were exposed to bereavement during their prenatal life. Children (primarily females) who were exposed to maternal bereavement due to traumatic father or sibling deaths had an increased risk of type 1 diabetes (relative risk [RR] 2.03, 95% CI 1.22–3.38) (300). While suggestive, these data need to be confirmed in a prospective study with exposures and outcomes ascertained at frequent intervals.

SOCIOECONOMIC FACTORS

The wide variation in childhood type 1 diabetes incidence rates within different populations could be partially explained by indicators of national and individual prosperity. An Italian study suggested that the association between early-life socioeconomic indicators and the risk of type 1 diabetes varied by age at onset of diabetes (301). These indicators could reflect differences in environmental risk factors, such as nutrition or lifestyle, that are important in determining the risk of type 1 diabetes. The EURODIAB study has shown a positive association of incidence rates with increasing value of gross domestic product (302).

OTHER FACTORS

Initiation of persistent islet autoimmunity may be related to factors operating during pregnancy, such as infections, preeclampsia, blood incompatibility, or during the perinatal period.

PRENATAL AND PERINATAL FACTORS

In utero and perinatal exposures may trigger islet autoimmunity. Viral infection of a fetus or newborn often evades clearance and may induce lifelong immunologic tolerance to the virus (303). The ability of the offspring's immune system to regard a virus as self may have consequences for latency, re-infection, and autoimmunity. Such a mechanism has been proposed for the role of enteroviruses and rubella virus in the etiology of type 1 diabetes.

Other potential risk factors include ABO incompatibility, hyperbilirubinemia, preeclampsia (304), complicated delivery (169,305), mother's age (306), and high birth weight for gestational age (305,306,307). In contrast, smoking in pregnant mothers was found to reduce type 1 diabetes risk (307). A systematic review and meta-analysis of 18 studies suggested that preterm birth was significantly associated with increased risk of type 1 diabetes (OR 1.18, 95% CI 1.11–1.25) (308). Subgroup analyses suggested the association was present both in case-control studies (OR 1.16, 95% CI 1.06–1.26) and cohort studies (RR 1.20, 95% CI 1.11–1.29). A large Swedish cohort study found an inverted U-shaped relation between gestational age and type 1 diabetes (309). Children born before the 33rd week or after the 40th week were at the lowest risk, while those born between 33 and 36 weeks were at the highest risk (RR 1.18, 95% CI 1.09–1.28), compared to those born at term. While these factors are unlikely to directly trigger islet autoimmunity, they may direct future research toward causal exposures.

Further evidence of fetal programming of type 1 diabetes risk comes from the still unexplained decreased type 1 diabetes risk in children of mothers with type 1 diabetes compared to children of fathers with type 1 diabetes (310,311).

GENE X ENVIRONMENT INTERACTIONS

The inconsistencies in the associations between dietary factors and islet autoimmunity or type 1 diabetes across studies may be explained, in part, by methodologic differences in population selection and data collection. However, another explanation is gene-environment interaction, where the differences in the observed exposure associations may be due to differences in gene allele frequency across populations. There are a number of ways to explore gene x environment interaction in epidemiologic data, each dependent on the underlying hypothesis.

One hypothesis is that the effect of environmental risk factors may be stronger among individuals possessing increased genetic risk variants; whereby the odds ratio (or relative risk) is significantly different than 1 (i.e., associated) in those possessing the genetic risk variants, such as the HLA-DR risk genotypes, and null (i.e., not associated) in those without the variants, perhaps because it is easier to see the effect of the exposure in a genetically susceptible population. Alternatively, the aforementioned rise in type 1 diabetes incidence, coupled with data suggesting an increasing penetrance of moderate-risk HLA-DR genotypes, suggests that the pressures of an increasingly permissive environment may be more easily observed

in children with moderate- or low-risk HLA-DR genotypes compared with high-risk genotypes.

In addition, one can examine a potential gene x environment interaction in more detail by dividing analyses into exposure*HLA combinations, with one risk group being those who have the exposure but not the HLA genotype, another risk group contains those who have the HLA genotype and not the exposure, and the putative highest risk group (i.e., representing the interaction) would be those with both the HLA genotype and the exposure. Each of these risk groups would be compared to the referent group, who are those with neither the HLA genotype nor the exposure. If the odds ratio in those with both the genetic variant and the exposure is greater than the product of the odds ratio for the exposure and odds ratio for the genotype, then the interaction is considered *more than multiplicative*.

Several studies have examined potential interactions between the HLA variants and dietary exposures. Stene *et al.* tested whether the effect of different dietary factors (use of cod liver oil and multivitamins by the mother during pregnancy, use of cod liver oil or vitamin D supplements in the first year of life, and exclusive breastfeeding for <3 months) differed across HLA risk groups and found no evidence of interaction, although power was limited (312). In DAISY, the hazard ratios for islet autoimmunity for early and late exposure to cereals in children with HLA-DR3/4 genotype were greater than in children with the moderate and low HLA-DR genotypes, although the interaction term was only marginally significant (168). Studies from Colorado and Chile have indicated a more than multiplicative joint effect of HLA-DR risk and either short duration of exclusive breastfeeding (313) or early introduction of cow's milk and solid foods (314). As an example, in the Colorado study, the odds ratio for type 1 diabetes for being HLA-DR3/4 in the absence of early exposure to solid foods was 3.1 (95% CI 1.4–7.2), the odds ratio for early exposure to solid foods in the absence of

FIGURE 11.5. Risk of Developing Islet Autoimmunity for Reported Intake of Omega-3 Fatty Acids. Interaction Between Intake of Alpha-Linolenic Acids and Polymorphisms of *FADS1* and *FADS2*, Diabetes Autoimmunity Study in the Young (DAISY), 2001–2008
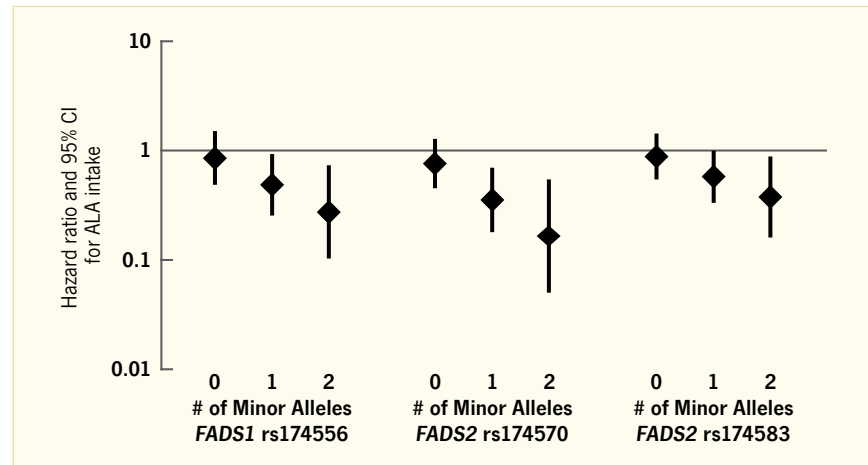
Hazard ratios calculated for a 1-standard deviation difference in omega-3 fatty acid levels, adjusted for human leukocyte antigen (HLA) genotype, family history of type 1 diabetes, and caloric intake. ALA, alpha-linolenic acid; CI, confidence interval.

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HLA-DR3/4 was 1.7 (95% CI 0.5–5.8), and the odds ratio for having both HLA-DR3/4 and early exposure to solid foods was 6.3 (95% CI 2.5–16.1) (314).

The inconsistent findings with childhood cow's milk consumption and risk of islet autoimmunity or type 1 diabetes may be due to the modifying effects of the underlying genetic profile. In DAISY, greater childhood cow's milk protein intake (as a surrogate of total milk consumption) was associated with increased islet autoimmunity risk in children with low/moderate-risk HLA-DR genotypes (HR 1.41, 95% CI 1.08–1.84), but not in children with high-risk HLA-DR genotypes (315).

In addition to HLA, other type 1 diabetes candidate genes, such as *INS, PTPN22, CTLA4,* and *IFIH1,* have been explored for interactions with dietary exposures. DIPP (316) detected an interaction between early cow's milk exposure, *PTPN22,* and appearance of islet autoimmunity, where the *PTPN22* polymorphism was associated with the development of islet autoimmunity only in children exposed to cow's milk formula prior to age 6 months.

Investigators have explored interactions with genes that are not candidate genes for type 1 diabetes but may be related to dietary exposures either with regard

to metabolism or action. For example, omega-3 fatty acids may act as ligands for the nuclear receptor peroxisome proliferator-activated receptor-gamma (PPARG) to promote anti-inflammatory actions. However, no evidence of interaction was found between the *PPARG* gene variant and cod liver oil intake on risk of type 1 diabetes in a Norwegian case-control study (317). Delta-6-desaturase, encoded by *FADS2,* and delta-5-desaturase, encoded by *FADS1* (318), work in series to convert the omega-3 fatty acid ALA to the more anti-inflammatory fatty acid EPA. DAISY observed a strong interaction between dietary intake of ALA and *FADS1* and *FADS2* on risk of islet autoimmunity, where ALA intake was significantly more protective for islet autoimmunity in the presence of the increasing number of minor alleles at *FADS1* rs174556 ($p_{interaction}$=0.017), at *FADS2* rs174570 ($p_{interaction}$=0.016), and at *FADS2* rs174583 ($p_{interaction}$=0.045) (Figure 11.5) (319). Thus, the putative protective effect of n-3 fatty acids on islet autoimmunity may result from a complex interaction between intake and genetically controlled fatty acid desaturation.

In BABYDIAB, cesarean section appeared to interact with immune response genes, such as the *IFIH1* gene, where increased risk for type 1 diabetes was only seen in

children who were delivered by cesarean section and had type 1 diabetes-susceptible *IFIH1* genotypes (12-year risk, 9.1% vs. <3% for all other combinations, p<0.0001)

(320). In Norway, mode of delivery was also found to interact with *PTPN22*, using a case-only approach, where the relative risks for type 1 diabetes conferred by

PTPN22 were 2.11 (95% CI 1.64–2.72) for those born vaginally and 0.99 (95% CI 0.50–1.99) for those born by cesarean section (p$_{interaction}$=0.028) (321).

ENVIRONMENT X ENVIRONMENT INTERACTIONS

Environmental exposures may also interact, or act in concert, with other environmental exposures; however, examples of these observations are not prevalent in the scientific literature. DAISY (322) observed that a greater number of gastrointestinal illnesses was associated with an increased risk of islet autoimmunity, but only among children who were exposed to gluten-containing grains (wheat or barley) either age <4 months (HR 1.37, 95% CI 1.22–1.55) or age ≥7 months (HR 1.12, 95% CI 1.05–1.19). Power to detect gene-environment or

environment-environment interactions has been limited in studies reported so far. Table 11.5 provides a summary of the significant associations with diet described above, including gene-diet and infection-diet interactions.

Prospective cohort studies have contributed enormously to the understanding of the natural history and risk factors for type 1 diabetes. A variety of exposures appear to trigger islet autoimmunity and to promote progression to clinical diabetes in some children; none of the

current candidate risk factors seems to explain most of the risk. Future trials may need to take into account the genetic and environmental heterogeneity of this disease in developing personalized interventions.

TABLE 11.5. Summary of Published Dietary Findings From Prospective Studies of Islet Autoimmunity and Type 1 Diabetes

DIETARY EXPOSURE	PREDICTORS OF INCREASED RISK OF ISLET AUTOIMMUNITY (STUDY) (REF.)	PREDICTORS OF RISK OF PROGRESSION TO TYPE 1 DIABETES IN CHILDREN WITH ISLET AUTOIMMUNITY (STUDY) (REF.)	PREDICTORS OF TYPE 1 DIABETES IN COHORT (STUDY) (REF.)
In utero diet	Low intake of vegetables in maternal diet during pregnancy (ABIS) (176)		
	Low intake of potatoes in maternal diet during pregnancy (DAISY) (177)		
Breastfeeding	Short breastfeeding duration (partial and exclusive) (ABIS) (174)		Infant not breastfed when first exposed to gluten (DAISY) (169)
	Infant not breastfed when first exposed to cereals (DAISY) (168)		
Cow's milk	No effect of cow's milk-based formula compared with hydrolysate formula in infancy (TRIGR) (183)	Increased childhood cow's milk consumption (DAISY) (315)	Increased cow's milk antibodies in infancy (TRIGR Pilot) (197)
	Increased childhood cow's milk consumption (DIPP) (184)		
	Gene-environment interaction: Increased childhood cow's milk consumption and HLA* (DAISY) (315)		
	Increased serum myristic acid, pentadecanoic acid, monounsaturated palmitoleic acid isomers 16:1 n-7 and 16:1 n-9, and conjugated linoleic acid (biomarkers of milk and ruminant meat fat intake) (DIPP) (191)		
	Gene-environment interaction: Early cow's milk formula exposure and *PTPN22*† (DIPP) (316)		
Solid foods and cereals	First exposure to cereals before age 3 months or not until after age 6 months (DAISY) (168)		First exposure to solid foods before age 4 months or not until after age 6 months (DAISY) (169)
	First exposure to gluten before age 3 months (BABYDIAB) (171)		First exposure to fruit before age 4 months (DAISY) (169)

Table 11.5 continues on the next page.

TABLE 11.5. (continued)

DIETARY EXPOSURE	PREDICTORS OF INCREASED RISK OF ISLET AUTOIMMUNITY (STUDY) (REF.)	PREDICTORS OF RISK OF PROGRESSION TO TYPE 1 DIABETES IN CHILDREN WITH ISLET AUTOIMMUNITY (STUDY) (REF.)	PREDICTORS OF TYPE 1 DIABETES IN COHORT (STUDY) (REF.)
	First exposure to root vegetables before age 4 months (DIPP) (173)		First exposure to rice/oat after age 6 months (DAISY) (169)
	First exposure to gluten between ages 5 and 5.5 months (compared with later), only for islet autoimmunity developing in the first 3 years of life (DIPP) (173)		
	Environment-environment interaction: Early and late exposure to gluten and increased number of gastrointestinal infections‡ (DAISY) (322)		
	Gene-environment interaction: First exposure to cereals before age 3 months or not until after age 6 months and HLA§ (DAISY) (168)		
	First exposure to egg before age 8 months (compared with after 11 months), only for islet autoimmunity developing in the first 3 years of life (DIPP) (173)		
Vitamin D	Low intake of vitamin D from foods in maternal diet during pregnancy (DAISY) (217)		No vitamin D supplementation in infancy (224)
	Low intake of vitamin D in maternal diet during pregnancy (ABIS) (218)		Low 25(OH)D levels in serum (DODSR) (227)
			Low serum 25(OH)D levels in mother during pregnancy (220)
Polyunsaturated fatty acids	Decreased omega-3 fatty acids in diet (DAISY) (13)		
	Gene-environment interaction: Decreased ALA intake and *FADS1/FADS2*‖ (DAISY) (319)		
	Decreased erythrocyte membrane omega-3 fatty acid levels (DAISY) (13)		
	Decreased erythrocyte membrane DPA levels (DAISY) (319)		
	Decreased serum ALA (DIPP) (191)		
Vitamin E			Low serum alpha-tocopherol (242)
Obesity, insulin resistance, and beta cell stress	Increased height growth velocity (DAISY) (278)	Increased height growth velocity (DAISY) (278)	Increased BMI in childhood (1970 British Birth Cohort) (276)
	Lower height (DAISY) (278)	Higher glycemic index of the diet (DAISY) (280)	
	Lower weight (DAISY) (278)		
	Higher weight (Australian BabyDiab) (277)		
	Increased BMI Z-score (Australian BabyDiab) (277)		

Data in the table include nested case-control studies within prospective cohort studies. 25(OH)D, 25-hydroxyvitamin D; ABIS, All Babies In Southeast Sweden; ALA, alpha-linolenic acid; BMI, body mass index; DAISY, Diabetes Autoimmunity Study in the Young; DIPP, Diabetes Prediction and Prevention Study; DODSR, U.S. Department of Defense Serum Repository; DPA, docosapentaenoic acid; HLA, human leukocyte antigen; TRIGR, Trial to Reduce IDDM in the Genetically at Risk.
* Increased childhood cow's milk consumption in the moderate-risk HLA group, not the high-risk group.
† Possessing the *PTPN22* polymorphism increases risk only in children exposed to cow's milk formula during early infancy.
‡ A greater number of gastrointestinal illnesses were associated with an increased risk of islet autoimmunity but only among children who were exposed to gluten-containing grains (wheat or barley) either age <4 months or ≥7 months compared with age 4–6 months.
§ Early and late exposure to cereals are more strongly associated with islet autoimmunity in children with HLA-DR3/4 genotype compared with those with the moderate- and low-risk HLA-DR genotypes (interaction term was marginally statistically significant).
‖ ALA intake is more protective in the presence of increasing number of minor alleles at *FADS1* and *FADS2*.

SOURCE: References are listed within the table.

LIST OF ABBREVIATIONS

25(OH)D . . . . . 25-hydroxyvitamin D
ALA . . . . alpha-linolenic acid
BB . . . . BioBreeding
BCG . . . . Bacillus Calmette-Guérin
BMI . . . . body mass index
CI . . . . confidence interval
CMV . . . . cytomegalovirus
DAISY . . . . Diabetes Autoimmunity Study in the Young
DHA . . . . docosahexaenoic acid
DiMe . . . . Childhood Diabetes in Finland Study
DIPP . . . . Diabetes Prediction and Prevention Study
EPA . . . . eicosapentaenoic acid
GAD . . . . glutamic acid decarboxylase
GWAS . . . . genome-wide association studies
HLA . . . . human leukocyte antigen
HOMA-IR . . . . . homeostasis model assessment of insulin resistance
HR . . . . hazard ratio
IA-2 . . . . insulinoma antigen 2
IFIH1 . . . . interferon-induced helicase C domain-containing protein 1
MIDIA . . . . Environmental Triggers of Type 1 Diabetes Study
OR . . . . odds ratio
PPARG . . . . peroxisome proliferator-activated receptor-gamma
RR . . . . relative risk
RT-PCR . . . . . . reverse transcription-polymerase chain reaction
TEDDY . . . . The Environmental Determinants of Diabetes in the Young
TRIGR . . . . Trial to Reduce IDDM in the Genetically at Risk
ZnT8 . . . . zinc transporter 8

DUALITY OF INTEREST

Drs. Rewers, Stene, and Norris reported no conflicts of interest.

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