CHAPTER 15

DIABETES IN YOUTH

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SUMMARY

Diabetes is the third most prevalent severe chronic disease of childhood and a leading cause of retinopathy, nephropathy, neuropathy, and coronary and peripheral vascular disease later in life. Diabetes diagnosed in youth, defined as age <18 years, and young adults is not always easy to classify into one of the main etiologic "types", i.e., type 1 or type 2. This is especially true since obesity, classically associated with type 2 diabetes, is now more common among youth with type 1 diabetes. Data suggest that youth with diabetes autoantibodies and obesity are metabolically similar to thin type 1 diabetic youth and do not have "type 1.5" or "double diabetes." The prevalence of diabetes in U.S. youth in 2009 was 2.2 per 1,000 overall; the prevalence of type 1 diabetes was 1.93 per 1,000 and that of type 2 diabetes was 0.24 per 1,000. Non-Hispanic white youth had the highest prevalence of type 1 diabetes, followed by non-Hispanic black youth. Type 2 diabetes was found to occur in all racial/ethnic groups, but the proportion of type 1 to type 2 diabetes varied greatly by race/ethnicity, with type 2 diabetes representing only 5.5% of cases of diabetes in non-Hispanic white youth, but 80% of diabetes in American Indian youth. Between 2001 and 2009, a 31% increase in prevalence of type 2 diabetes and a 21% increase in prevalence of type 1 diabetes were observed.

Risk factors for type 1 diabetes include genetics, especially the HLA region, and environmental factors, such as viruses and early life diet, though few nongenetic factors are well established. Type 2 diabetes risk factors include genetics, which explains only a small percentage of risk, intrauterine exposure to maternal obesity and diabetes, and high gestational weight gain, as well as postnatal obesity with rapid catch-up growth from low birth weight. Breastfeeding appears to reduce the risk of type 2 diabetes in youth.

The major complications of youth-onset diabetes were once thought to develop only after achieving adult age. Newer data suggest that with sensitive techniques, diabetic retinopathy, neuropathy, and elevated urine albumin concentrations can be detected after 3–5 years of diabetes duration. In addition, increased arterial stiffness, reduced heart rate variability (as a sign of cardiac autonomic neuropathy), and carotid artery wall thickening can also be detected and are associated with higher levels of glycemia. These subclinical and clinical outcomes appear to be more common among youth with type 2 than type 1 diabetes at the same duration. Cardiovascular disease risk factors (e.g., lipids, blood pressure, inflammatory and oxidative stress markers) are also elevated after short durations, especially in youth with type 2 diabetes or those with poor glycemic control. Mortality among youth with diabetes is elevated compared to nondiabetic controls by 30%–200%. Those with type 1 diabetes diagnosed before age 20 years have a life expectancy that is 15–27 years shorter than that of nondiabetic persons, although substantial improvements in life expectancy have been noted among those diagnosed after 1965. No life expectancy studies are available among youth with type 2 diabetes.

The earlier onset of both type 1 and type 2 diabetes results in a longer duration of diabetes at any adult age than in prior years. Thus, women with youth-onset diabetes are now more likely to have diabetes during their pregnancies, which results in increased offspring risk for both obesity and diabetes. In addition, complications development is duration dependent, so persons with youth-onset diabetes now face chronic kidney disease and dialysis, myocardial infarction, and stroke at younger ages than persons who develop diabetes as adults, resulting in greater life-years lost and higher health care costs. Since type 2 diabetes and many of the risk factors for complications in both types of diabetes cluster in youth who are economically disadvantaged, significant efforts to improve care will be required.

DEFINITIONS AND CLASSIFICATIONS OF DIABETES IN YOUTH

The initial classification of diabetes, developed in 1979 by an expert committee assembled by the National Institutes of Health (NIH), recommended the use of clinical characteristics, such as age of onset (juvenile vs. adult-onset) and method of treatment (insulin-dependent vs. non-insulin-dependent), to define type of diabetes (1). Over time, this classification system became unsatisfactory, due to the overlap in clinical characteristics and the widespread use of insulin treatment, regardless of presumed type of diabetes. Therefore, in 1997, the American Diabetes Association (ADA) convened a second

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expert committee (2) that proposed a physiologic framework to classify type of diabetes. The committee concluded that most diabetes cases fell into two broad categories: type 1 diabetes, an absolute deficiency of insulin usually due to autoimmune destruction of the pancreatic beta cells, and type 2 diabetes, a combination of insulin resistance and relative insulin deficiency. Rare forms of diabetes were combined and labeled "other diabetes types," including genetic defects of beta cell function, genetic defects of insulin action, and a variety of secondary forms of diabetes (see Chapter 6 *Other Specific Types of Diabetes*). Finally, a separate category was labeled "gestational diabetes," defined as any degree of glucose intolerance with onset or first recognition during pregnancy (see Chapter 4 *Gestational Diabetes*). This chapter focuses on the most common forms of pediatric diabetes: type 1 and type 2 diabetes in youth. Monogenic forms of diabetes that affect children, such as maturity-onset diabetes of youth and neonatal diabetes, are described in Chapter 7 *Monogenic Forms of Diabetes*.

TYPE 1 DIABETES IN YOUTH

Type 1 diabetes is believed to be caused by immune-mediated beta cell destruction leading to insulin deficiency. Symptoms are usually rapid in onset and include polyuria, polydipsia, weight loss, abdominal symptoms, headaches, and ketoacidosis. Insulin therapy is necessary for survival (3).

The autoimmune destruction of the beta cells is mediated by T cells and accompanied by the formation of autoantibodies, such as those against the 65 kD isoform of glutamic acid decarboxylase (GADA), those against the zinc transporter 8 (ZnT8A), insulinoma-associated-2 antibodies (IA-2A), insulin autoantibodies (IAA), and islet cell autoantibodies (ICA). These antibodies are present prior to the appearance of clinical disease and predict disease development (4,5,6). The presence of each antibody at diagnosis varies with age of onset, sex, and race/ethnicity (7,8,9), but one or more autoantibodies are typically present at diagnosis of type 1 diabetes in 80%–90% of affected children (3). If antibodies are present in the context of clear insulinopenia and ketosis, a diagnosis of autoimmune type 1 diabetes or type 1a diabetes is given. If patients have a clinical picture consistent with type 1 diabetes, but no antibodies are present, the ADA recognizes a category labeled type 1b diabetes (or idiopathic type 1 diabetes). Patients with type 1b diabetes tend to be older, are often of African or Asian descent, and have a greater body mass index (BMI, kg/m^2) than age-matched children with autoimmune type 1 diabetes (3). It is not clear whether these patients have a different underlying pathology or if they manifest autoantibodies that are not measured by common assays.

In 2006, because of concerns regarding lack of standardization of autoantibody assays among various laboratories, NIH convened an international committee of experts to ensure standardization of GADA and IA-2A measurements. This standardization was a significant step forward in ensuring correct classification of autoimmune-mediated diabetes (10).

TYPE 2 DIABETES IN YOUTH

Once thought to be a disease of adulthood, type 2 diabetes is increasingly recognized in children and adolescents, reportedly accounting for 20%–50% of new-onset diabetes cases in pediatric populations within the United States (11,12) and disproportionately affecting minority racial/ethnic groups, especially African Americans, South and East Asians, Pacific Island Natives, and American Indians/First Nation peoples (13,14,15,16,17,18). The increase in type 2 diabetes in youth is thought to be secondary to concurrent increases in obesity. This form of diabetes is primarily characterized by insulin resistance detected at the level of skeletal muscle, liver, and adipose tissues with a failure of beta cell compensation and a relative insulin deficiency (3). The extent to which children progress through stages of obesity, insulin resistance, and glucose intolerance to type 2 diabetes is not fully understood; however, the pathway to disease is much shorter and less predictable in children than in adults.

Pediatric patients with type 2 diabetes are usually overweight or obese (BMI ≥85th percentile for age and sex), and comorbidities, such as hypertension and dyslipidemia, can be present at diagnosis. Often there is a strong family history of diabetes in first and second degree family members. Weight loss at diagnosis is less common than in type 1 diabetes patients, and acanthosis nigricans is frequently identified on examination. Patients usually present with evidence of residual beta cell function, although no standardized cutoffs exist for insulin or C-peptide levels. These patients typically lack evidence of autoimmunity. Ketosis is less common than in type 1 diabetes, as individuals with type 2 diabetes usually produce enough insulin secretion to prevent lipolysis. Insulin may or may not be required at diagnosis or for long-term treatment of hyperglycemia, but insulin therapy is not required for survival (3).

LIMITATIONS AND CHALLENGES OF TRADITIONAL CLASSIFICATION APPROACHES

Because of clinical differences at the time of diagnosis, a presumptive clinical classification of patients as having type 1 diabetes or type 2 diabetes is possible, although not always clear cut. The weight distribution of children with type 1 diabetes is usually proportionate to the weight distribution in the general population (19,20). Thus, approximately 20%–40% of children with type 1 diabetes are now overweight (depending on race/ethnicity), though rarely as overweight as most youth with type 2 diabetes. The presence of acanthosis nigricans, hypertension, or hyperlipidemia at diabetes onset is most consistent with insulin resistance and type 2 diabetes. However, with hyperglycemia and insulinopenia, there is some degree of insulin resistance in patients with type 1 diabetes as well. Although family history is important, approximately 15% of African American youth with type 1 diabetes have a family history of type 2 diabetes. Likewise, patients with type 1 diabetes have a three times greater presence of type 2 diabetes in their families than does the general population (21). Although ketoacidosis is

more common with type 1 diabetes, up to 29% of patients with type 2 diabetes may have ketosis at disease onset because of hyperglycemia-induced beta cell toxicity, resulting in very low endogenous insulin/C-peptide levels (22). Therefore, C-peptide levels may be low at diagnosis of type 2 diabetes and may be normal during the honeymoon phase of type 1 diabetes and thus not helpful in classification at onset of diabetes (23).

Since the late 1990s, it has been noted that obese adolescents with a clinical picture suggestive of type 2 diabetes can present in ketoacidosis of varying degrees (22,24) or have evidence of autoimmunity (25). In such situations, due to the absence of standard case definitions, terms such as "type 1.5 diabetes," "double," "hybrid," or "mixed" diabetes have been used (26). Although not part of the ADA classification system, these terms are familiar to most endocrinologists and found in well-respected journals. The current ADA etiologic classification of diabetes poses important practical challenges for researchers and clinicians because it does not provide operational definitions for the markers used to define types of diabetes (i.e., autoimmunity, insulin resistance, insulin deficiency). Thus, no standard case definitions exist for epidemiologic research or surveillance of pediatric diabetes. In addition, the ADA framework assumes that there are two distinct types of diabetes, with little or no overlap. The reader is referred to Chapter 1 *Classification and Diagnosis of Diabetes* for additional discussion of this topic.

NOVEL APPROACHES TO CLASSIFICATION OF DIABETES IN YOUTH

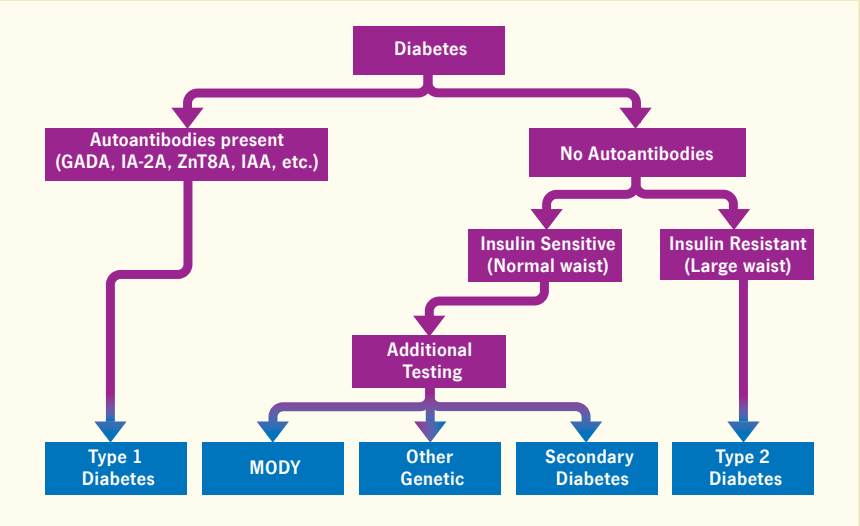
The SEARCH for Diabetes in Youth study (SEARCH) developed a novel approach to classify type of diabetes using the 1997 ADA framework (27) by operationalizing two main etiologic markers, *autoimmunity* and *insulin sensitivity*, to identify etiologic subgroups of youth with diabetes. Presence of autoimmunity was based on positive titers for either GADA (≥33 NIDDK U/mL) or IA-2A (≥5 NIDDK U/mL). Since many participants were treated with insulin, positive IAA was not included. Insulin sensitivity (IS) was estimated using the following equation: IS = exp [4.64725 - 0.02032*(waist, cm) - 0.09779*(A1c, %) - 0.00235*(triglyceride, mg/dL)], developed and validated by performing a euglycemic-hyperinsulinemic clamp study in a subset of diabetic participants and nondiabetic controls (28). The major component of the formula explaining 70% of the variance in measured glucose disposal rate was waist circumference. The study established the range of IS for nondiabetic youth by applying the equation to 2,860 multiracial youth age 12–20 years participating in the U.S. National Health and Nutrition Examination Surveys (NHANES) in 1999–2004, and insulin resistance was defined as an IS value below the 25th percentile (IS <8.15) for NHANES youth.

Participants were classified into four mutually exclusive groups: autoimmune and insulin sensitive, autoimmune and insulin resistant, non-autoimmune and insulin sensitive, and non-autoimmune and insulin resistant. The study then explored how other characteristics, including genetic susceptibility to autoimmunity, degree of insulin deficiency, and clinical factors, varied across these categories (27). There were several important findings. First, most youth with diabetes fell into categories that align with traditional descriptions of type 1 diabetes (autoimmune and insulin sensitive diabetes; 54.5%) and type 2 diabetes (non-autoimmune and insulin resistant diabetes; 15.9%). Importantly, the study provided evidence that the group classified as autoimmune and insulin resistant was likely to represent individuals with autoimmune type 1 diabetes and obesity, a phenotype that has expanded as a result of the recent increase in the frequency of obesity but is unlikely to be a distinct etiologic entity. This conclusion was based on several findings: (1) the phenotype represented approximately 26% of all autoimmune cases, a proportion similar to that expected, given that the definition of insulin resistance was based on the lowest 25th percentile in the general population; (2) the group had a similar prevalence and titers of diabetes-related autoantibodies and a similar distribution of human leukocyte antigen (HLA) DR-DQ risk genotypes to those observed in the autoimmune and insulin sensitive group, suggesting a similar contribution of immune-mediated disease processes; and (3) a follow-up study found a similar rate of decline of approximately 4% per month in fasting C-peptide levels over time in the two autoimmune groups (insulin sensitive and resistant) (29), lending additional support to the notions that type 1 diabetes is a distinct etiological category and that the main driver of beta cell loss is autoimmunity, regardless of prevailing insulin resistance that may occur simultaneously. There was also identified a group that had no evidence of autoimmunity and no evidence of insulin resistance (approximately 10% of all cases), which was deemed to require additional testing, including additional measurements of diabetes-related autoantibodies (of note, only two antibodies were measured) and testing for monogenic forms of diabetes to clarify etiology. Indeed, pilot data indicated that almost 20% of youth who were negative for GADA and IA-2A were, in fact, positive for ZnT8A (29) and that most cases with single-gene mutations in hepatocyte nuclear factor (HNF)1α, HNF4α, or glucokinase present with a phenotype consisting of insulin sensitivity and absence of autoimmunity (30).

Taken together, these findings suggest that standard case definitions can be operationalized to classify type of diabetes in youth (Figure 15.1) (31): type 1 diabetes is autoimmune diabetes, regardless of presence of obesity or insulin resistance, while type 2 diabetes requires absence of diabetes-related autoantibodies and presence of large waist circumference or insulin resistance (for example, based on the above equation). For the small proportion of patients who may not be able to be classified as proposed above, additional tests may be required. This approach has not yet been evaluated in other populations nor accepted by U.S. or international diabetes organizations as standard of practice.

SEARCH also found that provider-assignment of type of diabetes agreed well with the etiological assessment, at least for cases that fit the typical pictures of type 1 and type 2 diabetes (27). Therefore, for the purpose of public health surveillance of pediatric diabetes, use of provider-assigned type of diabetes collected from medical records, along with periodic validation using diabetes-related autoantibodies and waist circumference in a sample of representative cases, may represent an adequate and cost-effective case definition strategy.

FIGURE 15.1. Algorithm for Classification of Pediatric Diabetes



GADA, glutamic acid decarboxylase antibody; IA-2A, insulinoma-associated antibody 2; IAA, insulin autoantibody; MODY, maturity-onset diabetes of youth; ZnT8A, zinc transporter 8 antibody.

SOURCE: Reference 31, copyright © 2014 American Diabetes Association, reprinted with permission from the American Diabetes Association

BURDEN OF DIABETES AMONG U.S. YOUTH

The following sections of this chapter emphasize publications of North American studies (United States, Canada, Mexico) from 2000 to the present. Older publications are included when seminal or when little else was available. Publications from outside North America are included to help place American results in context, or when they present unique results, but their inclusion is not systematic.

Much of the knowledge of the burden of childhood type 1 diabetes has been generated by large collaborative efforts based on standardized registry data, such as the Diabetes Mondiale (DIAMOND) Project worldwide (32,33) and the EURODIAB Study in Europe (34,35). These registries showed that, while at the start of the 20th century, type 1 diabetes was rare and rapidly fatal, by the end of the century, a steady increase in incidence had been reported in many parts of the world (33). In addition, emerging data have indicated, also by the end of the century, that type 2 diabetes had become the major form of diabetes in young people in several nonwhite populations.

Nevertheless, epidemiologic data for temporal trends in pediatric diabetes, by type, are minimal for most of the global population of children, including North America. To address some of these needs, SEARCH, a multicenter epidemiologic study conducted in six U.S. centers (South Carolina, Ohio, Colorado [and selected American Indian reservations in Arizona and New Mexico], Washington, Hawaii, and Kaiser Permanente Southern California) that encompass the racial and ethnic diversity of the United States, was launched in the early 2000s. The registry was designed to estimate the prevalence and incidence of diabetes among U.S. youth age <20 years, according to type of diabetes, age, sex, and race/ethnicity, and to characterize selected acute and chronic complications of diabetes and their risk factors. In addition to SEARCH, the Philadelphia Pediatric Diabetes Registry has published incidence data on three racial/ethnic groups with type 1 diabetes since 1985. Other pediatric type 1 diabetes registries in the United States and Canada have also provided data, which are summarized below.

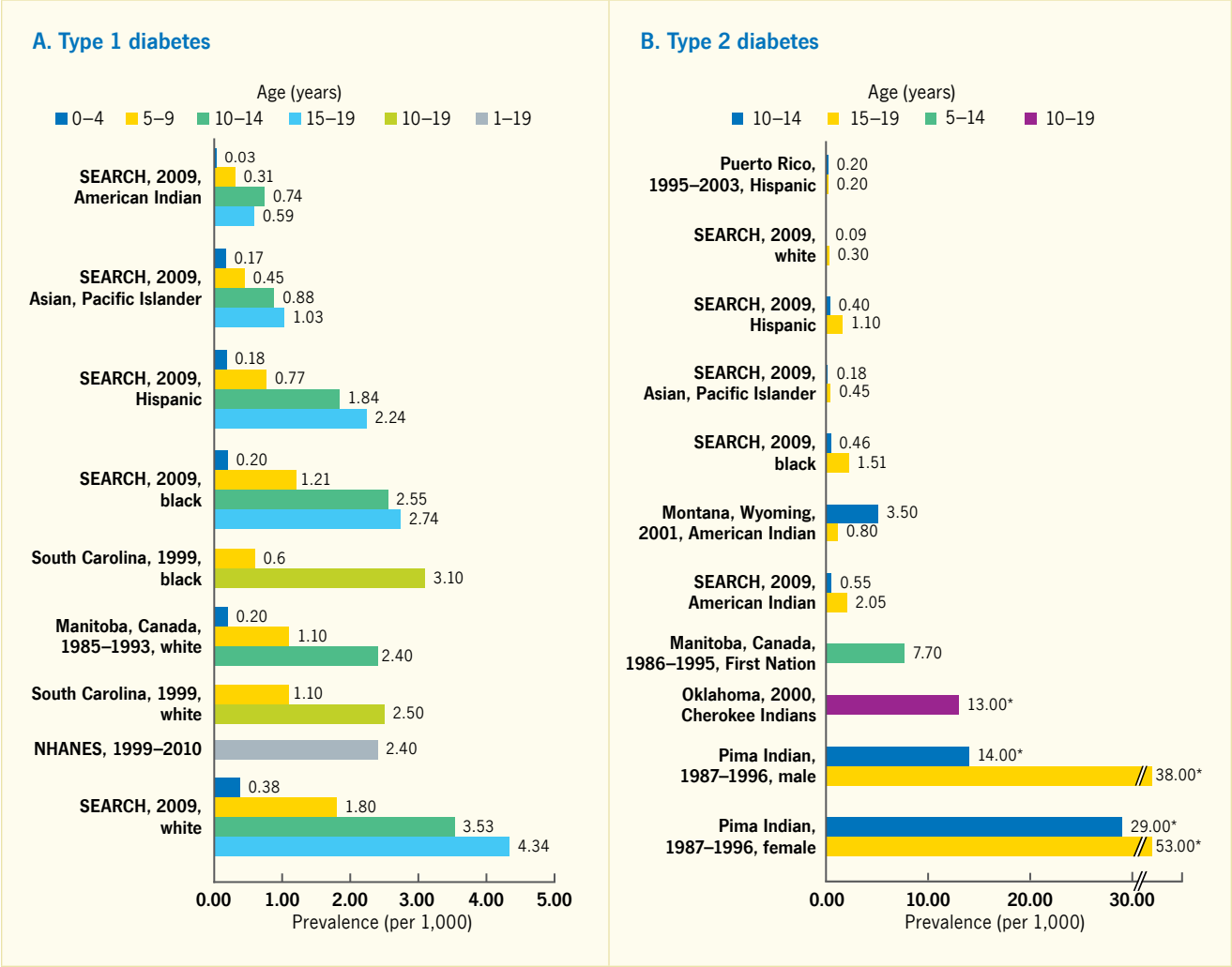
TYPE 1 DIABETES

The majority of epidemiologic data on type 1 diabetes are based on a clinical definition, including physician diagnosis and daily insulin injections (36). In addition, most European studies have limited the age range of populations to <15 years to avoid misclassification of type of diabetes. With the exception of SEARCH and the Philadelphia Registry (37), studies have assumed, but not confirmed via measured diabetes autoantibodies, that "type 1" diabetes is autoimmune-mediated diabetes. Selected data on prevalence, incidence, and trends in the incidence of type 1 diabetes in youth age <20 years from North American studies are summarized in this section, with a focus on race/ethnicity-specific estimates. A comprehensive overview is presented in Chapter 2 *Prevalence and Incidence of Type 1 Diabetes Among Children and Adults in the United States and Comparison With Non-U.S. Countries*.

Prevalence

Comparisons of prevalence data may not fully capture the impact of diabetes, since prevalence is determined not only by disease incidence, but also by case survival, which may vary across populations. Prevalence data, however, are useful in determining the public health impact of type 1 diabetes. Selected estimates of type 1 diabetes prevalence in different North American populations are shown in Figure 15.2A (38,39,40,41).

FIGURE 15.2. Prevalence of Diabetes Among Youth Age 0–19 Years, by Age and Race/Ethnicity



SEARCH, SEARCH for Diabetes in Youth study.
* All screened with fasting glucose or oral glucose tolerance test.

SOURCE: (A) References 38, 39, 40, 41; (B) References 14, 15, 38, 81, 82, 83

SEARCH identified 6,701 children with type 1 diabetes in 2009 among approximately 3.4 million ethnically diverse children age <20 years under surveillance. The prevalence of type 1 diabetes (per 1,000) was 1.93 per 1,000 overall (95% confidence interval [CI] 1.88–1.97) and varied with age and race/ethnicity, being lowest among American Indians (ranging from 0.03 at age 0–4 years to 0.59 at age 15–19 years), followed by Asians and Pacific Islanders (0.17 and 1.03, respectively), Hispanics (0.18 and 2.24, respectively), and African Americans (0.20 and 2.74, respectively), and highest among non-Hispanic whites (0.38 and 4.34, respectively) (38). An estimated 168,141 children/youth in the United States had type 1 diabetes in 2009 (38).

A report from Philadelphia found the overall prevalence of type 1 diabetes in youth age 0–14 years to be 1.58 per 1,000 with similar race/ethnicity patterns to those reported by SEARCH, but with substantially lower prevalence estimates overall and in each racial/ethnic group, likely due to the case ascertainment approach used (survey completed by school nurses) (37). Using data from the NHANES 1999–2010, Menke *et al.* estimated the prevalence of type 1 diabetes among youth of current age 1–19 years to be 2.4 per 1,000 (95% CI 1.7–3.3) (using either definition 1: insulin within 1 year of diagnosis and current use of insulin; diagnosed age <30 years, or definition 2: definition 1, but age <40 years at onset) (41). These definitions likely overestimate the prevalence of type 1 diabetes, since many persons with young-onset type 2 diabetes will also use insulin and/or have age of onset <30 or <40 years.

Incidence

Worldwide, the incidence of type 1 diabetes in children varies substantially with geographic location and age of onset, from <0.1 in China and Venezuela up to >40 per 100,000 per year in Scandinavian countries and Sardinia (36). While clear-cut differences in the occurrence of type 1 diabetes exist across geographic boundaries, likely reflecting different pools of susceptibility genes and/or different occurrence of environmental determinants of the disease, the clinical picture and the severity of the disease

remain constant (42). Thus, the observed differences in incidence throughout the world are unlikely to be confounded by misclassification of type of diabetes. Across all geographic areas, including in the United States, incidence peaks at ages 5–9 and 10–14 years (36). The early peak is possibly caused by increased exposure to diabetogenic factors related to school entry. The incidence peak at puberty may be related to increases in levels of sex hormones and associated increase in insulin resistance or to alterations in lifestyle and associated changes in the pattern of infections.

Much of the variation in the incidence of type 1 diabetes may be due to different race/ethnicity distributions of various populations throughout the world (43). Caucasians tend to be at greater risk for type 1 diabetes compared to all other race/ethnicity groups. The reasons for this remain elusive; however, different frequencies of high-risk genes are a likely contributor. Among U.S. youth, non-Hispanic whites are about 1.5 times as likely to develop type 1 diabetes as African Americans or Hispanics, four times as likely as Asians and Pacific Islanders, and almost nine times as likely as American Indians (Figure 15.3A) (40,44,45,46,47,48,49,50). Since 2002, approximately 5.5 million children age <20 years (about 6% of the <20-year-old U.S. population) have been under surveillance each year by SEARCH to estimate incidence of type 1 diabetes by age of onset and race/ethnicity. Based on these data from 2002–2005, the incidence (per 100,000 per year) of type 1 diabetes is highest in non-Hispanic whites (19.4 at age 0–4 years; 30.1 at age 5–9 years; 32.9 at age 10–14 years; and 11.9 at age 15–19 years) (50), followed by African Americans (12.0, 19.3, 21.3, and 9.5, respectively) (49) and Hispanics (10.2, 18.2, 18.4, and 8.7, respectively) (47), and lowest among Asians and Pacific Islanders (5.2, 7.6, 9.1, and 5.7, respectively) (45) and American Indian youth (1.2, 3.3, 1.9, and 4, respectively) (44). It was estimated that 15,600 youth in the United States are diagnosed with type 1 diabetes annually (51).

Temporal Trends

Most (52,53,54,55,56), but not all (57,58,59,60), population-based registries have shown an increasing incidence of type 1 diabetes over time. The DIAMOND project examined the trends in incidence of type 1 diabetes from 1990 to 1999 in 114 populations from 57 countries. Based on 43,013 cases of type 1 diabetes from a study population of 84 million children age ≤14 years (33), the average annual percent change in incidence over this time period was 2.8% (95% CI 2.4%–3.2%). Similarly, the EURODIAB study, a large European survey including 20 population-based registries in 17 countries, showed a 3.2% (95% CI 2.7%–3.7%) average annual percentage change for the period 1989–1998 (35) and a 3.9% (95% CI 3.6%–4.2%) increase from 1989 to 2003 (61). Interestingly, the observed incidence rates confirmed, and in fact exceeded, the incidence predicted for 2010 by earlier projections (62). In EURODIAB (61), estimates of the rates of increase were highest in the youngest age group (5.4%, 95% CI 4.8%–6.1%, for age 0–4 years).

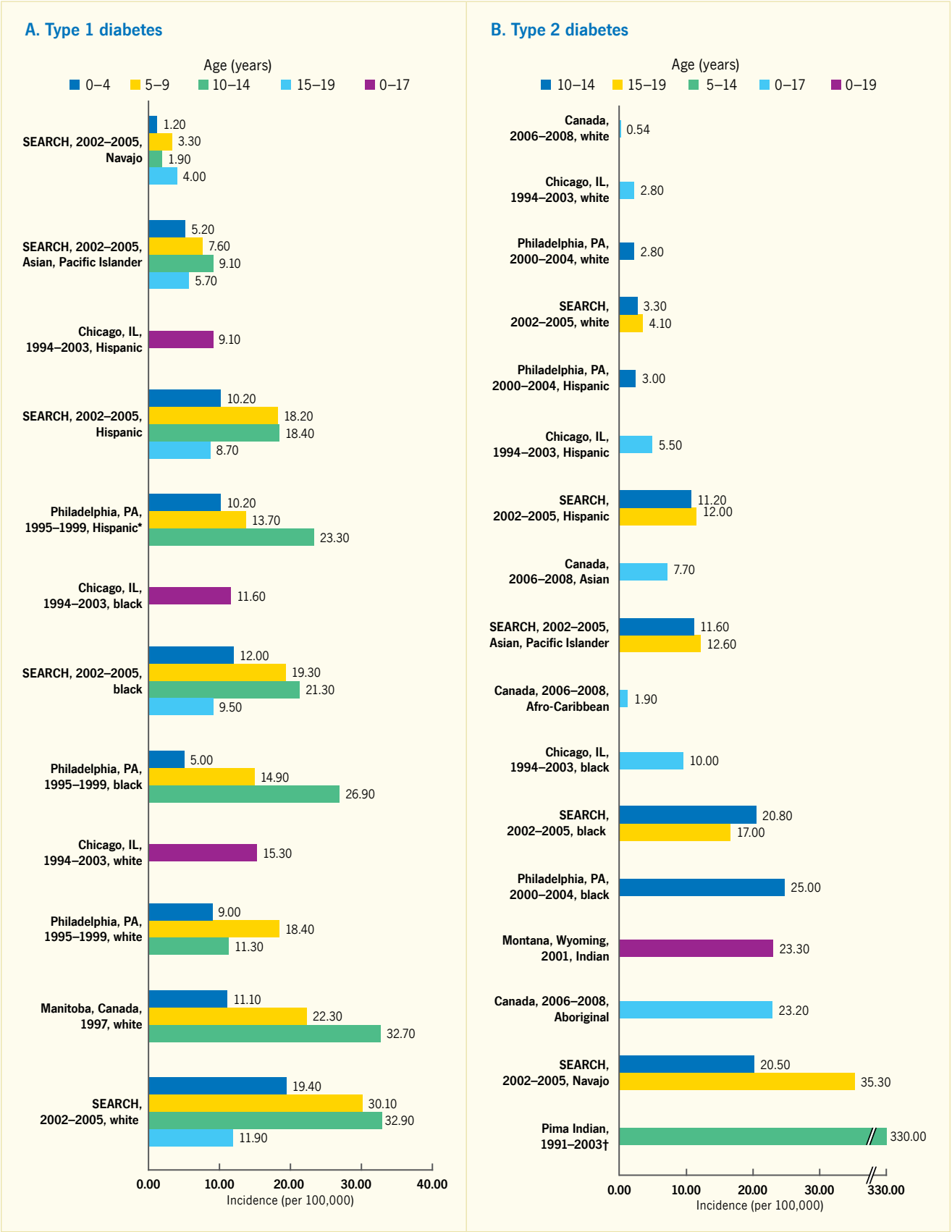
Data from the United States, where registry efforts have been less coordinated than in Europe, suggest similar trends (Figure 15.4A) (46,63,64,65,66,67,68,69). While the United States stood apart from other parts of the world in reporting a stable incidence of childhood type 1 diabetes in the 1970s through the 1990s (70), SEARCH reported that the 2002–2005 incidence of type 1 diabetes in non-Hispanic white youth age ≤14 years was 27.5 per 100,000 per year (50), a rate that exceeds the incidence predicted for 2010 from older data (62). Between 2002 and 2009, the incidence of type 1 diabetes among non-Hispanic white youth in SEARCH increased annually by 2.7% (95% CI 1.9%–3.6%) (68). Using data from the Colorado IDDM Registry and the SEARCH Colorado site, the incidence of type 1 diabetes was shown to have increased by 2.3% (95% CI 1.6%–3.1%) per year in youth age ≤17 years from 1978 to 2004 (63). Of note, the increase was significant for both non-Hispanic white (2.7% per year, 95% CI 1.9%–3.6%, p<0.0001) and Hispanic youth (1.6% per year, 95% CI 0.2%–3.1%, p<0.013). Similar to the EURODIAB data, in Colorado, the increase in incidence was highest among the 0–4-years age group (3.5%, 95% CI 2.1%–4.9%, per year). Additional evidence of increasing incidence of type 1 diabetes come from registries in Philadelphia (48,67,71,72), Chicago (73), and Allegheny County (64), which reported increasing trends in non-Hispanic white (average annual percentage change range 1.1%–2.7%), African American (average annual percentage change range -1.4%–3.2%), and Hispanic youth (average annual percentage change 0.9%–4.7%).

Changes in prevalence of type 1 diabetes in the United States have also been reported (74). In 2001, 4,958 of 3.3 million youth were diagnosed with type 1 diabetes for a prevalence of 1.48 per 1,000 (95% CI 1.44–1.52). In 2009, 6,666 of 3.4 million youth were diagnosed with type 1 diabetes for a prevalence of 1.93 per 1,000 (95% CI 1.88–1.97). In 2009, the highest prevalence of type 1 diabetes was 2.55 per 1,000 among non-Hispanic white youth (95% CI 2.48–2.62) and the lowest was 0.35 per 1,000 in American Indian youth (95% CI 0.26–0.47). Type 1 diabetes increased between 2001 and 2009 in all sex, age, and race/ethnicity subgroups, except for those with the lowest prevalence (age 0–4 years and American Indians). There was a 21.1% (95% CI 15.6%–27.0%) increase in type 1 diabetes over 8 years.

Projections

Based on data collected over 15 years, the EURODIAB study projected that between 2005 and 2020, the number of new cases with type 1 diabetes in European children age <5 years will double, and the prevalence in those age ≤14 years will increase by 70% (61). In the United States, projections suggest that the number of youth with type 1 diabetes age <20 years may increase by 23% by 2050, even if incidence of type 1 diabetes remains stable (75). However, if incidence continues to rise at the levels described above, the number of youth with type 1 diabetes may increase more than threefold in the United States, especially among minority youth (75).

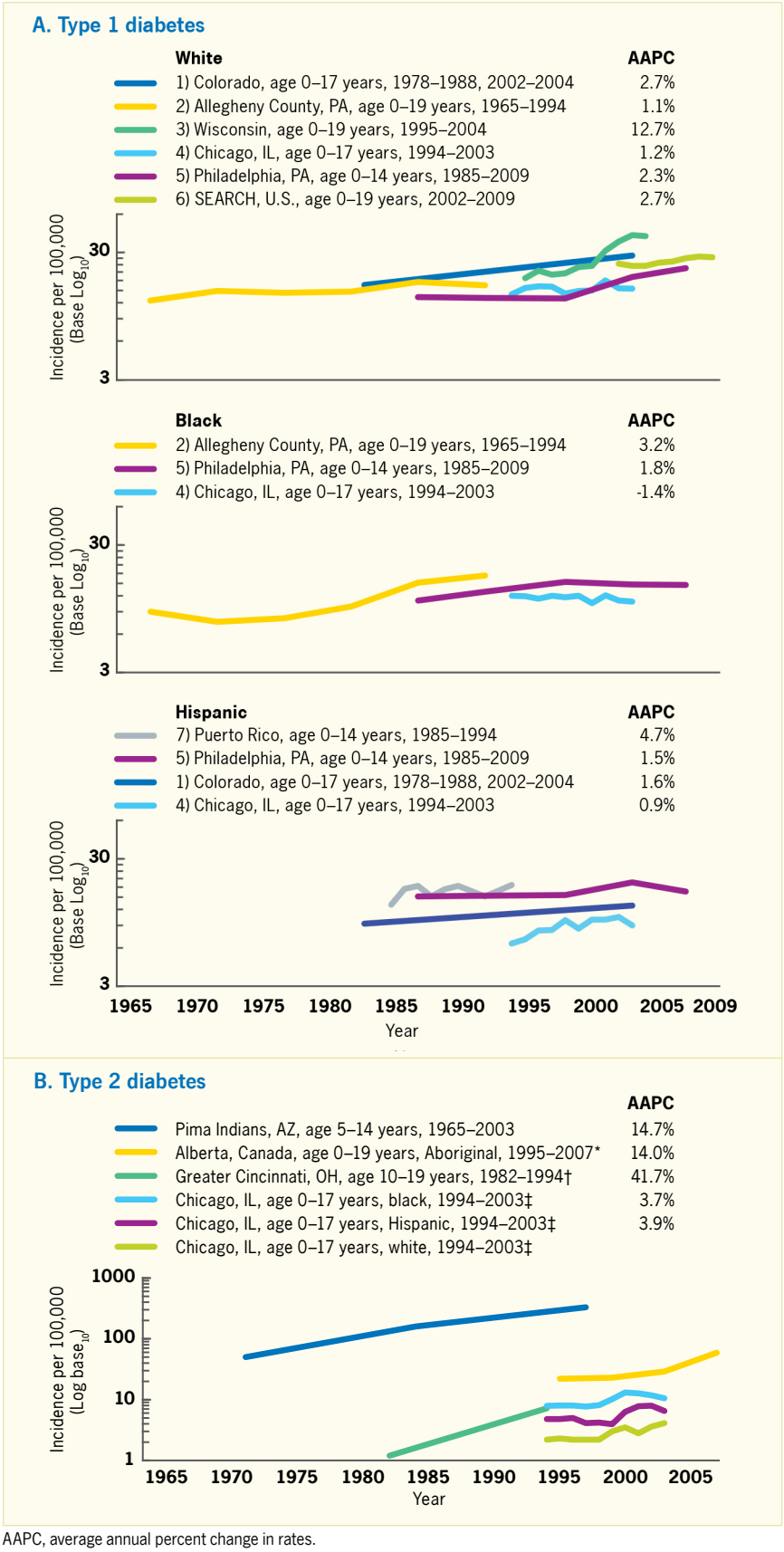
FIGURE 15.3. Incidence of Diabetes Among Youth Age 0–19 Years, by Age and Race/Ethnicity



SEARCH, SEARCH for Diabetes in Youth study
* Hispanic: largely Puerto Rican
† All screened with oral glucose tolerance test.

SOURCE: (A) References 40, 44, 45, 46, 47, 48, 49, 50; (B) References 44, 45, 46, 47, 49, 50, 67, 82, 84, 85

FIGURE 15.4. Temporal Trends in Incidence of Diabetes Among Youth Age 0–19 Years, by Race/Ethnicity, 1965–2009



AAPC, average annual percent change in rates.

* Diabetes type not specified

† Cincinnati: 68% black, 32% white

‡ Chicago: "non-type 1 diabetes"

SOURCE: (A) References 46, 63, 64, 65, 66, 67, 68, 69; (B) References 46, 66, 85, 89, 90

TYPE 2 DIABETES

Type 2 diabetes has been traditionally viewed as an adult disease, with risk increasing with advancing age and duration of obesity. An increasing proportion of youth with apparent type 2 diabetes has been reported since the late 1990s, especially in minority populations (76,77). The epidemiology of type 2 diabetes in youth is yet unclear, due to its relative rarity, the lack of standard clinical and epidemiologic definitions, and the small number of appropriate, population-based studies. Selected data on prevalence, incidence, and trends in the incidence of type 2 diabetes in youth age <20 years from North American studies are summarized, with a focus on race/ethnicity-specific estimates. A comprehensive overview of type 2 diabetes is presented in Chapter 3 *Prevalence and Incidence of Type 2 Diabetes and Prediabetes*.

Prevalence

Population-based studies, where all individuals within a geographic area undergo diabetes screening, are ideal to determine prevalence, as they capture even undiagnosed cases. However, among the limited number of available population-based studies of type 2 diabetes in youth, few test oral glucose tolerance, and many lack key data essential to differentiate type 2 diabetes from type 1 diabetes.

In the United States, the NHANES III provided data on self-reported diabetes in a sample of 2,867 12–19-year-olds, collected between 1988 and 1994 (78). Thirteen adolescents had diabetes, of whom four were classified as type 2 diabetes, implying a type 2 diabetes prevalence of 0.013 per 1,000. All four with presumed type 2 diabetes were of non-Hispanic African American or Mexican American origin. An additional 22 adolescents had glycosylated hemoglobin (A1c) >6.0% (>42 mmol/mol) but did not meet the formal criteria for diabetes. The differentiation between type 1 diabetes and type 2 diabetes was based only on the use of insulin, likely underestimating the type 2 diabetes prevalence, as many youth with type 2 diabetes are also treated with insulin.

More recent U.S. data were available from the NHANES 1999–2002, using the same definitions of diabetes (79). The prevalence of diabetes was 0.05 per 1,000 among more than 4,000 adolescents completing self-report information. Of these cases, 44% were classified as type 2 diabetes, implying a prevalence of 0.02 per 1,000. Among more than 1,400 NHANES subjects with fasting glucose measures, the prevalence of impaired fasting glucose was 11% using a cutoff of 100 mg/dL (5.55 mmol/L), but only 1.5% using a cutoff of 110 mg/dL (6.11 mmol/L), unchanged from NHANES III. Unfortunately, no data were provided on undiagnosed diabetes. However, limited data from screening studies in diverse populations suggest that undiagnosed type 2 diabetes is relatively rare in youth (80). In addition, the use of self-report has obvious limitations, as does the poor differentiation between type 1 diabetes and type 2 diabetes.

Figure 15.2B (14,15,38,81,82,83) provides estimates of type 2 diabetes prevalence among North American youth, by race/ethnicity, from population-based studies not based on self-report. SEARCH identified 806 youth age <20 years with provider-diagnosed type 2 diabetes in 2009, in a population of 3.4 million youth (38). Among diabetic youth age <10 years, only 11 had type 2 diabetes. Among those ≥10 years, the highest prevalence of type 2 diabetes (per 1,000) was observed among American Indian youth (0.55 at age 10–14 years and 2.05 at age 15–19 years), followed by African Americans (0.46 and 1.51, respectively), Asians and Pacific Islanders (0.18 and 0.45, respectively), and Hispanics (0.4 and 1.10, respectively), while the lowest prevalence was seen in non-Hispanic whites (0.09 and 0.30, respectively) (38). Lower rates of type 2 diabetes prevalence were seen in a survey of Philadelphia school nurses, where non-Hispanic whites had a prevalence of 0.03 per 1,000, African Americans 0.28 per 1,000, and Hispanics 0.05 per 1,000 (37). An estimated 19,147 children/youth in the United States had type 2 diabetes in 2009 (38).

A limited number of other population-based studies of childhood type 2 diabetes prevalence exist. Most have been conducted in American Indians (15,82,83) and showed high prevalence of type 2 diabetes. Thirty years of data collected among the Pima Indians of Arizona have shown extremely high and increasing prevalence of type 2 diabetes: from 1967–1976 to 1987–1996, the type 2 diabetes prevalence in Pima Indian youth increased from 24 to 38 per 1,000 in males and from 27 to 53 per 1,000 in females, the highest rates reported in youth to date. Of note, this was a screened population (14).

Incidence

A summary of population-based studies reporting on incidence of type 2 diabetes in North American youth in the United States and Canada is provided in Figure 15.3B (44,45,46,47,49,50,67,82,84,85). Although a variety of age groupings were used, there is a remarkable consistency across registries with respect to incidence rates by race/ethnicity. In general, non-Hispanic whites are about three times less likely to develop type 2 diabetes than Hispanic and Asian and Pacific Islander youth, about six times less likely than African Americans, and almost 12 times less likely than American Indian youth. Among SEARCH youth age <10 years, most had type 1 diabetes, regardless of race/ethnicity, with only 19 with type 2 diabetes (51). Confirming previous reports, type 2 diabetes accounted for a substantial proportion of all diabetes cases in minority youth age ≥10 years, especially American Indians (86.2%) and Asians and Pacific Islanders (69.7%), but also among African Americans (57.8%) and Hispanics (46.1%). Based on data from 2002–2005, the rates of type 2 diabetes (per 100,000 per year) were the highest among American Indian youth (20.5 and 35.3 for ages 10–14 and 15–19 years, respectively), followed by African American (20.8 and 17.0, respectively), Asian and Pacific Islander (11.6 and 12.6, respectively), and Hispanic youth (11.2 and 12.0, respectively), and were lowest among non-Hispanic whites (3.3 and 4.1, respectively) (51). The annual number of newly diagnosed youth with type 2 diabetes in the United States was approximately 3,700. Of note, the highest incidence rates of (screen-detected) type 2 diabetes in youth were reported by the Pima Indian study: 330 per 100,000 per year (85).

These data suggest that pediatric type 2 diabetes is mainly a feature of high-risk ethnic groups. However, well-designed studies of youth in Germany, Austria, France, and the United Kingdom (86,87,88) indicate that type 2 diabetes remains a rarity, accounting for only 1%–2% of all pediatric diabetes cases. In contrast, while the SEARCH data (51) support the notion that type 2 diabetes in youth is predominantly occurring in high-risk ethnic groups, type 2 diabetes accounted for 14.9% of all diabetes cases among non-Hispanic white adolescents age ≥10 years. Although differences in obesity rates between U.S. and European youth are likely contributors, the full explanation for these discrepancies deserves further study.

Temporal Trends

Few data exist on temporal trends in the incidence of type 2 diabetes in youth (Figure 15.4B) (46,66,85,89,90), and most studies rely on data collected from diabetes clinics. A strength of such studies is that assignment of type of diabetes is likely to be more accurate than in population-based studies, although not always uniform. However, a clinic population may not accurately represent the general population.

Several clinic-based studies reported an increasing incidence of type 2 diabetes. For example, among 1,027 consecutive patients attending a Cincinnati, Ohio, diabetes clinic (90), type 2 diabetes incidence increased tenfold, from 0.7 per 100,000 per year in 1982 to 7.2 per 100,000 per year in 1994 (average annual percentage change 41.7%). Onset was typically around puberty, the female:male ratio was 1.7:1, and the majority were African Americans. Similarly, type 2 diabetes incidence rates reportedly rose by 3.7%, 3.9%, and 9.6% per year, respectively, from 1994 to 2003, among African American, Hispanic, and non-Hispanic white children with insulin-treated,

"non-type 1" diabetes in Chicago (46,66). The incidence was higher in African Americans and Hispanics than in non-Hispanic whites, with a female predominance.

Population-based studies reporting trends in the incidence of type 2 diabetes in youth to date are based on Native populations. Among Aboriginal youth in Alberta, Canada (89), a 14% annual increase was reported between 1995 and 2007 in youth age <20 years. While type of diabetes was not specified, it was assumed that virtually all was type 2 diabetes. Interestingly, a similar increase of 14.7% per year in screening-detected type 2 diabetes in youth age 5–14 years was reported by the Pima Indian study for the period 1965–2003 (85).

SEARCH reported on trends in prevalence of type 2 diabetes from 2001 and 2009 (74). In 2001, 588 of 1.7 million youth were diagnosed with type 2 diabetes for a prevalence of 0.34 per 1,000 (95% CI 0.31–0.37). In 2009, 819 of 1.8 million were diagnosed with type 2 diabetes for a prevalence of 0.46 per 1,000 (95% CI 0.43–0.49). In 2009, the prevalence of type 2 diabetes was 1.20 per 1,000 among American Indian youth (95% CI 0.96–1.51); 1.06 per 1,000 among African American youth (95% CI 0.93–1.22); 0.79 per 1,000 among Hispanic youth (95% CI 0.70–0.88); and 0.17 per 1,000 among non-Hispanic white youth (95% CI 0.15–0.20). Significant increases occurred between 2001 and 2009 in all age groups, both sexes, and in non-Hispanic white, African American, and Hispanic youth, with no significant changes for Asians and Pacific Islanders and American Indians. There was a 30.5% (95% CI 17.3%–45.1%) overall increase in type 2 diabetes over the 8-year period.

Projections

Projections on burden of type 2 diabetes in youth in the future provide a disturbing picture (72). The models project that by 2050, even at current incidence rates, the number of youth with type 2 diabetes may increase by almost 50%, essentially due to the minority population growth projected by the U.S. Census. However, if the incidence of type 2 diabetes increases, the number of youth with type 2 diabetes may increase more than fourfold (75).

RISK FACTORS FOR DIABETES IN YOUTH

TYPE 1 DIABETES

Genetic susceptibility plays a large role in type 1 diabetes, with the HLA genotypes (DR and DQ genes) explaining approximately 40%–50% of type 1 diabetes risk (91). The genetic variation can explain part of the geographic variation in incidence, but increased transmission of type 1 diabetes susceptibility is unlikely to explain the increasing trend over time of incidence of type 1 diabetes. Studies exploring potential temporal changes in the frequency and/or distribution of HLA genotypes associated with type 1 diabetes susceptibility found a decreasing frequency of high-risk HLA genotypes over time in individuals diagnosed with type 1 diabetes (92,93,94,95). These data suggest that the increase in type 1 diabetes since the 1950s–1960s is not likely due to increased incidence among those at the highest genetic risk in the HLA region, but rather, the result of a more permissive environment resulting in increased penetrance of low/moderate risk HLA genotypes or other genetic loci, or interactions between environmental risk factors and non-HLA genes. For additional information, the reader is referred to Chapter 12 *Genetics of Type 1 Diabetes*.

Several environmental factors are involved in the disease etiology, as extensively described in Chapter 11 *Risk Factors for Type 1 Diabetes*. This section briefly summarizes the risk factors most relevant for type 1 diabetes in youth. They are hypothesized to operate through a variety of mechanisms, including triggering an autoimmune response, overloading the beta cells and promoting apoptosis, or through alterations in the intestinal microbiome. However, few studies have explored whether changes in exposures to such risk factors may be responsible for the steady increase in type 1 diabetes worldwide. Longitudinal, collaborative efforts, such as The Environmental Determinants of Diabetes in the Young (TEDDY) study, following children at risk for type 1 diabetes from birth onwards, allow comparisons among different populations (United States, Finland, Germany, and Sweden) with different background incidence rates, different lifestyles, and environmental trends; these studies are expected to identify major environmental triggers of autoimmunity and type 1 diabetes.

Viruses and Immunizations

Viruses have long been considered a major risk factor for type 1 diabetes (96). The hypothesis is that in susceptible individuals, viral infections may trigger autoimmunity and accelerate the autoimmune destruction of beta cells leading to type 1 diabetes (97). Many studies have focused on human enteroviruses, with some finding positive associations between enterovirus infections and risk of type 1 diabetes or evidence that the seasonal variation seen with type 1 diabetes risk coincides with the time of enterovirus infections (96). However, prospective studies in Finland (Diabetes Prediction and Prevention [DIPP]) and Colorado (Diabetes Autoimmunity Study in the Young [DAISY]) reported opposing findings concerning the association between enterovirus infections and antibody titers with islet autoimmunity and type 1 diabetes: a positive association in DIPP (98), but no association in DAISY (99). Thus, the role of viral infections in the etiology of type 1 diabetes remains controversial.

Although childhood immunizations have been suggested to be associated with an increased type 1 diabetes risk, large population-based studies have found no associations (100,101) or even a protective effect (102,103). Moreover, some evidence suggests that lack of exposure to viruses or other infectious agents in early life may actually increase risk of type 1 diabetes, mainly due to decreased immune stimulation. The microbial environment has changed over the last 50

years; antibiotic use has increased, while exposure to enteroviruses, helminthes, and commensal bacteria has decreased (104). Consequently, the "hygiene hypothesis" proposes that the decreasing early life exposure to infectious agents in westernized societies has led to impairment in the maturation of the immune system, thus permitting an increased occurrence of immune-mediated disorders, such as asthma and type 1 diabetes (105)—a hypothesis that requires further testing.

Early Life Diet

Important changes in early life diet and feeding patterns worldwide over the last century have renewed the interest in early life nutrition as a possible explanation for the increasing incidence of type 1 diabetes. Breastfeeding and early exposure to cow's milk have been the most extensively studied, with conflicting findings suggesting both a protective effect of exclusive breastfeeding, as well as little or no association (43,106). It was hypothesized that early introduction of cow's milk or other solid foods may be detrimental, rather than breastfeeding itself being protective. These studies were limited by significant between-study heterogeneity and other methodologic problems. To adequately address the effect of infant diets on risk of type 1 diabetes, the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study, a collaborative international study group of 77 clinical centers in 15 countries, is conducting a clinical trial to address the role of breastfeeding versus cow's milk and risk of autoimmunity and type 1 diabetes (107,108). Pilot results have suggested that weaning to a highly hydrolyzed formula decreased by ~50% the cumulative incidence of one or more diabetes-related autoantibodies up to age 10 years (108). The trial will be completed when the last recruited child turns 10 years of age in 2017.

Few studies have focused on other practices of infant feeding, such as early exposure to solid foods. Although only limited research exists, positive associations between early exposure to solid foods, such as cereals or gluten-containing foods, and risk of type 1 diabetes have been reported (109,110). Some researchers believe that early exposure to cereal products or other solid foods might increase an immune response, which could trigger beta cell destruction (109,110), while others hypothesize that overfeeding early in life might lead to accelerated weight gain, resulting in beta cell overload and failure in the face of an autoimmune attack (111). Finally, early life exposure to dietary gliadin, a glycoprotein implicated in the intestinal damage associated with celiac disease, increases the risk of autoimmunity and type 1 diabetes through mechanisms involving both increased gut permeability and altered intestinal microflora (112). This novel and promising area of research is being explored in several longitudinal studies.

Early Life Growth

A trend toward an earlier age at diagnosis of type 1 diabetes, with stable or decreasing rates later in life (113,114,115,116), has been reported, suggesting that the increasing incidence of type 1 diabetes in youth is the result of an "acceleration" of disease onset to earlier ages rather than an increased lifetime risk (117). The accelerator (118) and the overload hypotheses (111) both propose that environmental risk factors prevalent in contemporary societies may accelerate the onset of type 1 diabetes (to younger ages) by increasing the demand for insulin production and thus overloading the beta cells. While the overload hypothesis has a broader perspective on the potential environmental factors in question (accelerated growth, infections, stress, and climate), the accelerator hypothesis focuses on body fatness and associated insulin resistance as the main accelerators.

Indeed, the prevalence of obesity has been increasing dramatically in Europe, the United States, and throughout the developed world over the past decades (119), and overweight is now present at increasingly younger ages (120). Prospective data from population-based studies in Europe (121) and the United States (122) have shown that children who later developed type 1 diabetes have faster growth trajectories before autoimmunity (122) and diagnosis of diabetes (121,122) and especially in the first years of life. Some studies have demonstrated an inverse association between age at type 1 diabetes diagnosis and childhood BMI, a surrogate measure of insulin resistance (123,124). SEARCH reported that a higher BMI was associated with a younger age at diagnosis with type 1 diabetes, but only in youth with substantially reduced beta cell function (123), suggesting that obesity may operate after initiation of autoimmunity, resulting in an accelerated beta cell decline that leads to an earlier type 1 diabetes diagnosis. Conversely, the Australian Baby Diab Study reported that weight gain early in life (birth to age 2 years) independently predicted the development of islet autoimmunity in a genetically at-risk population (125), an effect not seen in other studies (67). These data may be interpreted to suggest that changes in early life environmental factors, such as improved early life nutrition or overnutrition, or fewer early life infections, may lead to accelerated growth patterns in contemporary children. Accelerated growth, in turn, may overload the beta cells and/or trigger an autoimmune process in genetically predisposed individuals, thus resulting in an earlier presentation with type 1 diabetes.

TYPE 2 DIABETES

Since type 2 diabetes in youth is relatively new and relatively rare, there are very limited data on genes associated with early-onset type 2 diabetes (126). By virtue of their earlier age at onset, youth with type 2 diabetes may have higher frequencies of risk alleles than those seen with adult-onset cases. Many studies show a strong family history among affected youth, with 45%–80% having at least one parent with diabetes, and 74%–100% having a first or second degree relative with type 2 diabetes (76). Therefore, genetic factors are likely to play an important role in the risk for type 2 diabetes in youth. However, family history does not always imply a genetic cause, as factors such as similar environmental influences within families and the effects of the intrauterine environment on the

offspring also demand consideration. Risk factors for type 2 diabetes are described in detail in Chapter 13 *Risk Factors for Type 2 Diabetes* and Chapter 14 *Genetics of Type 2 Diabetes*; this section focuses on risk factors that are most relevant for type 2 diabetes in youth.

Obesity, Diet, and Physical Activity

In adults, the risk of type 2 diabetes increases with increasing weight (127), weight gain (128), BMI (127), waist-to-hip ratio (129), and central fat deposition (130,131). The rise in type 2 diabetes in youth is believed to have paralleled the increasing prevalence of overweight in North American youth and worldwide. NHANES III (1988–1994) revealed that 20% of children age 12–17 years were ≥85th percentile BMI for age (when only 15% would be expected) and 8%–17% had BMI ≥95th percentile (when only 5% would be expected), depending on race/ethnicity (19,132). The Bogalusa Heart Study of 11,564 children, adolescents, and young adults age 5–24 years found a mean weight increase of 0.2 kg per year with a twofold increase in overweight from 1973 to 1994 (133). The U.S. National Longitudinal Survey of Youth, a prospective cohort study, found that the prevalence of overweight increased annually from 1986 to 1998 by 3.2% in non-Hispanic white youth, by 5.8% in African Americans, and by 4.3% in Hispanics. Thus, by 1998, 12.3% of non-Hispanic white youth, 21.5% of African Americans, and 21.8% of Hispanics were overweight (19). During 1999–2000, 15% of 6–19-year-olds were overweight compared to 11% in 1994–1998, with the greatest increases in African American and Mexican American adolescents (134). In 2003–2004, 17.1% of U.S. children and adolescents were overweight (135). In addition, the heaviest children were much heavier than previously, with the greatest increases taking place in the top decile (135). Obesity has been increasing in Native populations, such as the Ojibwa-Cree community in Canada, where 48%–51% of children age 4–19 years were overweight (15). Mean relative weight of Pima Indian boys and girls has also increased over time ($p<0.0001$), especially among the heavier children (14). Changes in traditional lifestyles among indigenous communities, such as a reduction in hunting and gathering, and an increased adoption of sedentary lifestyles and westernized diets are thought to contribute to the rising obesity levels (136).

Obesity is likely linked to changes in children's diets (137,138). Fast food and high fat/high sugar food consumption have increased, while time for family meals has decreased in many societies. Moreover, a survey of California public schools found that 85% sold fast food, which in turn accounted for 70% of all food sales (139). Increases in snacking (with increased nutrient density of snacks, including soft drinks) were observed in nationally representative data from >20,000 U.S. 2–18-year-olds during 1973–1994 (140,141). While diet composition may contribute to obesity, the most important aspect in the development of type 2 diabetes in youth is likely to be excess caloric intake relative to caloric expenditure.

Concurrent with changes in diet, physical activity has decreased among children and adolescents (142). In 2011, only 29% of high school students surveyed had participated in at least 60 minutes per day of physical activity on all seven days before the survey (143). One reason for the decline in physical activity is the reduction of physical education in schools, with participation rates down from 41.6% in 1991 to 24.5% in 1995 and 31% in 2011 (143,144). In the developed world, increasing use of computers and television also markedly decrease children's activity level (135,138), as do lack of safe places to play, lack of organized sports, and fewer children walking to school.

Early Life Factors

While postnatal lifestyle is the most immediate cause of obesity, the intrauterine environment is increasingly recognized as an important contributor to disease both in childhood and in adult life. The influence of the maternal *in utero* environment is evidenced in the U- or J-shaped relationship between birth weight and adult obesity and metabolic disease, demonstrating that both nutritionally limited and excessive *in utero* environments can lead to postnatal obesity and type 2 diabetes later in life (145,146). Developmental biology has revealed the role of a mismatch between a constrained prenatal and a plentiful postnatal environment in the pathogenesis of obesity, i.e., "thrifty" obesity pathway (147). This is likely operating in developing countries and populations undergoing rapid transition. Another developmental pathway to obesity, likely more important in Western societies, is the fetal overnutrition pathway, resulting from exposure to maternal diabetes and/or obesity *in utero*. This pathway reflects the effects of hypernutrition during fetal life and creates the conditions for the later pathophysiologic effects of an obesogenic environment (147). Both genetic and environmental factors are likely to be involved in mediating these relationships.

Fetal Overnutrition. Several reports have convincingly shown that exposure to maternal diabetes *in utero* is a significant risk factor for obesity, impaired glucose tolerance, and type 2 diabetes in youth (148). The offspring of women with diabetes during pregnancy are more obese during childhood and adolescence, as demonstrated by the longitudinal follow-up of offspring of diabetic Pima Indian women (149,150,151). The offspring of diabetic women were large at birth, and at every age before 20 years, they were heavier for height than the offspring of prediabetic or nondiabetic women. Consequently, at every age before 20 years, offspring of Pima Indian diabetic women had more type 2 diabetes than those of prediabetic and nondiabetic women (152). The higher prevalence of type 2 diabetes was only partially mediated by the earlier development of obesity in these offspring (153). Similarly, Silverman *et al*. (154) followed a cohort of offspring of diabetic mothers and found that by age 8 years, almost half of the offspring had a weight >90th percentile. At age 12.3 years, these offspring of diabetic mothers had a significantly higher prevalence of impaired glucose tolerance

than an age- and sex-matched control group (19.3% vs. 2.5%), and two offspring had developed type 2 diabetes. A direct correlation was found between amniotic fluid insulin concentration at weeks 32–34 of pregnancy and obesity at ages 6 and 8 years, suggesting a possible mechanism of this excessive weight gain (155).

While intrauterine exposure is often difficult to separate from genetic factors, obesity and type 2 diabetes in offspring of diabetic mothers are not solely due to genetics. To determine the role of exposure to the diabetic intrauterine environment while controlling for genetic susceptibility, mean BMI and prevalence of type 2 diabetes were compared in Pima Indian siblings age <20 years born before and after their mother developed diabetes (156). BMI was significantly higher (+2.6 kg/m^2) in the 62 siblings born after their mothers were diagnosed with type 2 diabetes (exposed to the diabetic intrauterine environment) than in the 121 age-matched siblings born before. Similarly, within the same Pima Indian family, siblings born after the mother's diagnosis of diabetes had over a threefold higher risk of developing diabetes at an early age than siblings born before the diagnosis of diabetes in the mother (odds ratio [OR] 3.7, p<0.02).

Among Pima Indian youth, exposure to maternal diabetes and obesity in pregnancy accounted for most of the dramatic increase in type 2 diabetes prevalence over the previous 30 years (14). A similar finding was seen in other race/ethnicity groups (non-Hispanic white, African American, and Hispanic), where exposure to maternal diabetes and obesity together contributed to 47% of type 2 diabetes in the offspring (157).

Breastfeeding. In population-based studies, breastfeeding is protective against later development of obesity and type 2 diabetes (158,159). Even as infants, bottle-fed babies have significantly higher plasma insulin levels and a prolonged insulin response to glucose (160). In Pima Indians, exclusive breastfeeding for the first 2 months of life protected against the development of type 2 diabetes in adolescence and young adulthood (OR 0.64, 95% CI 0.4–0.9) (161), which was also seen in a group of youth of diverse racial/ethnic backgrounds (162). The prevalence of breastfeeding (any duration) was lower among youth with type 2 diabetes than among controls, and thus, breastfeeding was associated with significantly lower odds of type 2 diabetes (OR 0.26, 95% CI 0.15–0.46). Thus, for offspring of pregnancies that carry a high risk for future obesity, early infant diet may represent an opportunity to influence long-term consequences. Of note, the Exploring Perinatal Outcomes among Children (EPOCH) study in Colorado demonstrated that offspring who were exposed to maternal gestational diabetes and were breastfed for ≥6 months had lower overall and central adiposity measures at an average age of 10 years compared to those breastfed for <6 months (163). Taken together, these data suggest that breastfeeding may also attenuate the increased risk of type 2 diabetes associated with *in utero* overnutrition, a hypothesis that requires further testing.

COMPLICATIONS OF DIABETES IN YOUTH

In children and adolescents with diabetes, acute complications are more common than chronic complications, and at this age, they carry a greater risk of morbidity and mortality (164). Data on the occurrence of both acute and chronic complications are crucial to evaluate the effectiveness of diabetes education and management programs and to identify subgroups at increased risk. This section summarizes data on acute and chronic complications of diabetes in North American youth, specifically focusing on comparing youth with type 1 and type 2 diabetes. More comprehensive coverage is provided in *Diabetes in America* Section II *Complications of Diabetes and Related Conditions*.

ACUTE COMPLICATIONS

The major acute complications of diabetes in youth are diabetic ketoacidosis (DKA) and hypoglycemia. Table 15.1 summarizes studies of the occurrence of DKA and hypoglycemia in North American youth with diabetes.

Diabetic Ketoacidosis

DKA is a serious, costly, and potentially preventable complication caused by insulin deficiency. If left untreated, it can lead to coma and death. DKA may be present at clinical presentation of both type 1 and type 2 diabetes (165) and can also occur in individuals with established diabetes. The biochemical criteria for the diagnosis of DKA usually include hyperglycemia (blood glucose >11 mmol/L [>200 mg/dL]) with a venous pH <7.3 and/or a bicarbonate level <15 mmol/L. Glycosuria, ketonuria, and ketonemia are also present. These criteria are reasonably standardized across multiple studies.

Type 1 Diabetes. Clinic-based (166,167,168,169) and population-based studies (45,47,49,50,170) have reported a prevalence of DKA at onset of type 1 diabetes ranging from 25% to >30% across ages 0–19 years. DKA prevalence is higher at younger ages (<5 years) (166,167,168,170), and higher prevalence is usually associated with minority race/ethnicity, lower family income and education, and lack of health insurance (45,47,49,50,170). The T1D Exchange Clinic Registry found that after adjustment for socioeconomic status, more black participants experienced DKA and severe hypoglycemic events in the previous year than white or Hispanic participants (both p<0.001) (171,172).

In pediatric patients with established type 1 diabetes, the incidence of DKA after diagnosis ranged from 4 to 12 per 100 person-years (Table 15.1) (173). Data from the T1D Exchange Clinic Registry (172) of >13,000 type 1 diabetic youth across the United States found a similar prevalence of at least one episode

TABLE 15.1. Occurrence of Diabetic Ketoacidosis and Hypoglycemia Among Persons With Youth-Onset Diabetes

REFERENCE	POPULATION; YEARS	CRITERIA	OUTCOME	COMMENTS
DIABETIC KETOACIDOSIS				
Type 1 diabetes				
174	DCCT, randomized trial; 195 T1 youth age 13–17 years at trial entry; randomized to intensive vs. conventional insulin therapy; 1984–1993	Symptoms, serum ketones, or greater than or equal to moderate urinary ketones; arterial pH <7.30, or venous pH <7.25, or HCO_3 <15 mEq/L; and medical treatment	Incidence of DKA per 100 person-years Intensive ..... 2.8 Conventional 4.7	Randomized trial; adolescent DKA rate higher than in adults; these results are only for adolescents in the DCCT.
168	New York Children's Hospital, NY; 139 new-onset T1 youth age <18 years at onset; 1995–1998	Hyperglycemia, with ketosis and pH <7.3	Prevalence of DKA by age (years) at onset 0–18 ..... 38.0% 0–5 ..... 54.5% 6–10 ..... 31.3% 11–18 ..... 29.8%	Single hospital case series; not population-based; delay in diagnosis increased DKA prevalence 2.8-fold.
173	Barbara Davis Center, CO; 1,243 T1 youth age <19 years at last visit; median age at exam was 13.0 years; followed for 3.5 years; 1996–2000	Episode of hyperglycemia and ketoacidosis from emergency department visit or hospitalization, excluding at onset	Incidence of DKA per 100 person-years by sex and age (years) at last visit All ..... 8.0 Age — Boys — Girls <7 ..... 7.0 — 4.0 7–12 ..... 4.9 — 8.0 ≥13 ..... 7.5 — 12.0	Clinic-based; includes ~80% of state cases; predictors of DKA included higher A1c and reported insulin dose (all children) and underinsurance and psychiatric disorder (older children).
169	Colorado, 683 T1 youth with onset at age <18 years, 1998–2001; trend data from population-based IDDM Registry; 1978–1982	pH <7.3 or HCO_3 <15 mEq/L and hyperglycemia	Prevalence of DKA by period of diabetes diagnosis 1978–1982 ..... 38.0% 1998–2001 ..... 29.0%	Data from 1978–1982 population-based, but limited record review for laboratory; 1998–2001 data from single center covering ~80% of cases in Colorado. Hospitalization at onset dropped from 88% to 46% with little change in DKA.
166	Barbara Davis Center, CO; 359 new-onset T1 youth age <18 years at onset; 2002–2003	Any DKA pH <7.3 HCO_3 <15 mmol/L Severe DKA pH <7.10 HCO_3 <5 mmol/L	Prevalence of DKA at diabetes onset Any DKA ..... 28.4% Age (years) <4 ..... 55.2% 4–8 ..... 20.2% 9–12 ..... 25.4% 13–18 ..... 23.6% Uninsured/severe DKA ..... 50.0% Insured/severe DKA 30.6%	Clinic-based; includes ~80% of state cases.
167	Boston Children's Hospital, MA; 223 T1 youth age <6 years, hospitalized at onset; 1990–1999	Glucose >300 mg/dL, venous pH <7.3, and/or serum HCO_3 or total CO_2 <15 mmol/L by chart review	Prevalence of DKA at age of onset <6 years ... 43.7%	Single hospital case series, including cases transferred from other hospitals.
45, 47, 49, 50, 170	SEARCH, six U.S. centers; 1,656 new-onset T1 youth age <20 years at onset; 77% with chart review; 2002–2005	≥1 criteria: a. HCO_3 <15 mmol/L or pH <7.25 (venous) or <7.3 (arterial); b. ICD-9 code 250.1; or c. diagnosis of DKA in medical chart; all with hyperglycemia	Prevalence of DKA by race/ethnicity and age (years) at onset All ..... 29.4% White 0–4 ..... 28.9% 5–9 ..... 18.5% 10–14 ..... 24.0% 15–19 ..... 15.8% Black 0–9 ..... 30.8% 10–14 ..... 25.9% 15–19 ..... 16.7% Hispanic 0–9 ..... 25.6% 10–14 ..... 23.7% 15–19 ..... 21.6% Asian 0–19 ..... 27.9% Pacific Islander 0–19 ..... 33.3% American Indian 0–19 ..... 26.1%	Population-based; no difference by sex. Adjusting for center, age, sex, and race/ethnicity, DKA was associated with lower family income, less health insurance, and lower parental education.

Table 15.1 continues on the next page.

TABLE 15.1. (continued)

REFERENCE	POPULATION; YEARS	CRITERIA	OUTCOME	COMMENTS
186	TEDDY study in four countries compared to SEARCH (U.S.), German, Swedish, and Finnish registries; new-onset T1 youth ages <2 and <5 years; 2004–2010	Multiple definitions; most common: pH <7.3 or HCO_3 <15 mmol/L. If pH and HCO_3 missing, then urine ketones >40 mEq/L, blood ketones >3 mmol/L, or physician diagnosis of DKA.	Prevalence of DKA by age (years) of onset <2 <5 SEARCH (U.S.) 50.0% 36.4% Germany 54.0% 32.2% Sweden 39.5% 16.9% Finland 44.8% 18.7% TEDDY 15.0% 11.3%	TEDDY is an early-onset study of etiology of type 1 diabetes; close follow-up during study said to reduce DKA risk. TEDDY is not population-based; other registries are population-based.
172	T1D Exchange Clinic Registry; 13,487 T1 youth with age of onset <26 years and duration ≥2 years; median diabetes duration 6.0 years; 2010–2012	Self- or family report of hospitalization for DKA in prior year	Prevalence of ≥1 DKA episode in past year by current age (years) <6 9.4% 6–12 7.6% 13–17 11.4% 18–25 10.5%	Voluntary U.S. clinic-based registry; higher DKA among females, higher A1c, nonwhite race/ethnicity, lower income, and lack of private insurance.
185	SEARCH, five U.S. centers; 5,615 new-onset T1 youth age <20 years at onset; 78% with chart review; 2002–2010	≥1 criteria: a. HCO_3 <15 mmol/L or pH <7.25 (venous) or <7.3 (arterial); b. ICD-9 code 250.1; or c. diagnosis of DKA in medical chart; all with hyperglycemia	Prevalence of DKA at onset by diagnosis year 2002–2003 30.2% 2004–2005 29.1% 2008–2010 31.1%	Population-based
184	Pediatric Diabetes Consortium, seven specialty centers in the United States; 805 T1 youth with age of onset <19 years; 2009–2011	DKA: pH <7.3 or HCO_3 <15 mEq/L	Total 34.0% Across centers 28%–40% (p=ns)	Not population-based; ≥1 antibodies required; younger age, lack of private insurance, African American race, lower parental education, and not living with parents had higher risk.
Type 2 diabetes				
22	Cincinnati Children's Hospital, OH; 42 new-onset T2 youth age <20 years and negative ICA; mean age 14 years; 1982–1995	pH <7.3, HCO_3 <15 mEq/L, and glucose >250 mg/dL with ketonuria	Onset prevalence of DKA by sex and race All 28.6% Male 35.7% Female 12.1% White 0.0% Black 41.4% Asian 0.0%	Authors report this is a population-based series.
16	Little Rock, AR; pediatric tertiary care hospital; 50 T2 youth age 8–19 years at diagnosis; 1988–1995	Clinical chart review; serum ketones moderate-large	Prevalence of DKA 16.0%	Clinic-based series; 74% of T2 youth were black.
23	Canadian aboriginal (First Nation) T2 youth in Winnipeg, Manitoba, Children's Hospital; 118 T2 youth with age of onset 0–18 years; 1986–1999	DKA: pH ≤7.35, HCO_3 ≤15 mEq/L and hyperglycemia T2: no insulin treatment for >6 months and typical clinical presentation	Onset prevalence of DKA 4.2%	Hospital-based; female preponderance with DKA.
187	Toronto Hospital for Sick Children, Canada; 44 T2 youth with age of onset <18 years; 1994–2002	DKA not defined. T2: typical course and ≥2 risk factors (obesity, insulin resistance-related signs)	Onset prevalence of DKA 8.0%	Hospital-based; higher in African Canadians and South/East Asians. No DKA in white, Hispanic, or First Nation youth.
45, 47, 49, 50, 170	SEARCH, six U.S. centers; 507 new-onset T2 youth age 0–19 years; 77% with chart review	≥1 of criteria: a. HCO_3 <15 mmol/L or pH <7.25 (venous) or <7.3 (arterial); b. ICD-9 code 250.1; or c. diagnosis of DKA in medical chart; all with hyperglycemia	Onset prevalence of DKA by age (years) and race/ethnicity All 9.7% White 10–14 8.8% 15–19 2.6% Black 10–14 10.9% 15–19 13.1% Hispanic 10–14 9.4% 15–19 6.4% Asian 10–19 6.3%	Population-based; no difference by sex.

Table 15.1 continues on the next page.

TABLE 15.1. (continued)

REFERENCE	POPULATION; YEARS	CRITERIA	OUTCOME	COMMENTS
185	SEARCH, five U.S. centers; 1,425 new-onset T2 youth age <20 years at onset; 74% with chart review; 2002–2010	≥1 criteria: a. HCO_3 <15 mmol/L or pH <7.25 (venous) or <7.3 (arterial); b. ICD-9 code 250.1; or c. diagnosis of DKA in medical chart; all with hyperglycemia	Onset prevalence of DKA by diagnosis year 2002–2003 ..... 11.7% 2004–2005 ..... 6.3% 2008–2010 ..... 5.7%	Population-based; p for trend=0.005.
HYPOGLYCEMIA				
Type 1 diabetes				
174	DCCT; 195 T1 youth age 13–17 years at trial entry; randomized to intensive vs. conventional insulin therapy; 1984–1993	Severe hypoglycemia requiring assistance, and with coma/seizure by self- or family report	Incidence of hypoglycemia per 100 person-years Severe Intensive ..... 85.7 Conventional ..... 27.8 Severe with seizure/coma Intensive ..... 26.7 Conventional 9.7	Randomized trial
189	Wisconsin; 415 T1 youth with age of onset <20 years; current age 4–34 years; followed for 4.0–6.4 years from 1987–1992 to 1996	Self- or family reported frequency and severity of insulin reactions. Frequent: 2–4 times/week Severe: lost consciousness, hospitalized	Prevalence of insulin reactions by diabetes duration (years) 4.0 / 6.5 Frequent ..... 33% / 35% Severe ..... 7% / 4%	Original cohort population-based; mostly white, with health insurance; higher risk for severe hypoglycemia among youth age >5 years; intensive insulin therapy and lower A1c were also associated with frequent hypoglycemia.
173	Barbara Davis Center, CO; 1,243 T1 youth age <20 years at exam; followed a median of 3.3 years; 1996–2000	Loss of consciousness or seizure with emergency department visit or hospitalized	Incidence of severe hypoglycemia per 100 person-years by age (years) and sex at exam All ..... 19 Age: Boys / Girls <7 ..... 23 / 24 7–12 ..... 22 / 19 ≥13 ..... 20 / 14	Clinic-based; includes about 80% of state cases; predictors of severe hypoglycemia included longer duration, underinsurance (all children), and lower A1c, and psychiatric disorders in older children.
175	SEARCH, six U.S. centers; 2,743 T1 youth with age of onset <20 years and ≥1 year duration; mean diabetes duration 5 years; 2001–2007	Severe hypoglycemia: self-report of seizure, glucagon use, needing assistance, emergency department or hospitalization	Prevalence of ≥1 hypoglycemic episode in a 6-month period by type of insulin delivery Insulin pump ..... 10.3% MDI Glargine/rapid ..... 13.7% MDI Glargine/rapid+other ..... 12.5% MDI no Glargine ..... 11.4% 1–2 injections no Glargine 13.5%	50% of population-based cases had research visit; A1c lowest in pump-treated group; pump use was most common among whites with higher income, education, and private insurance.
191	Joslin Diabetes Center, Texas Children's Hospital cohort; 255 T1 youth 9–15 years at entry and duration ≥1 year; median 1.2 years follow-up 2004–2009 in overlapping waves	Hypoglycemia requiring assistance, and with coma/seizure (DCCT definition) by self- or family report	Incidence of hypoglycemia per 100 person-years Severe All ..... 37.6 NPH insulin ..... 46.1 Insulin pump ..... 31.8 Severe with seizure/coma All ..... 9.6 NPH insulin ..... 14.4 Insulin pump 4.5	Clinic-based; adjusted odds ratio for NPH insulin vs. insulin pump 2.9 (95% CI 1.1–7.6) for seizure/coma; no difference by age, sex; nonsevere hypoglycemia increased with duration.
190	Princess Margaret Hospital, Perth, Western Australia; 656 T1 youth age 6 months to 19 years at visit, with duration at least 6 months; 2008	Physician-validated severe hypoglycemia; no other criteria listed; hypoglycemia unawareness by validated questionnaire score ≥4	Incidence of severe hypoglycemia per 100 person-years All ..... 24.5 With hypoglycemia unawareness ..... 37.1 Without hypoglycemia unawareness 19.3	Hospital-based; estimated to include 79% of all patients in region.
172	T1D Exchange Clinic Registry; 13,487 T1 youth with age of onset <26 years and diabetes duration ≥2 years; median duration 6.0 years; 2010–2012	Self- or family report of seizure or loss of consciousness in prior year	Prevalence of ≥1 severe hypoglycemic episode in past year by current age (years) <6 ..... 9.6% 6–12 ..... 5.2% 13–17 ..... 6.3% 18–25 ..... 6.9%	Voluntary U.S. clinic-based registry; more common among blacks, families with lower income and no private insurance, longer duration, and using MDI. A1c was significant univariately, not multivariately.

A1c, glycosylated hemoglobin; CI, confidence interval; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; HCO_3, bicarbonate; ICA, islet cell autoantibodies; ICD-9, International Classification of Diseases, Ninth Revision; MDI, multiple daily injections; ns, nonsignificant; SEARCH, SEARCH for Diabetes in Youth study; T1, type 1 diabetes; T2, type 2 diabetes; TEDDY, The Environmental Determinants of Diabetes in the Young study.

SOURCE: References are listed within the table.

of hospitalization for DKA in the past year. They also found higher DKA rates among females, those with higher A1c, nonwhite race, lower income, and lack of private insurance (172). The Diabetes Control and Complications Trial (DCCT) randomized participants with type 1 diabetes to intensive (multiple daily insulin injections or pumps) or to usual care. Among adolescents in the trial, intensive glycemic control decreased the incidence of DKA by approximately 40% (p=0.17) (174), though absolute rates were only 2.8 (intensive) to 4.7 (conventional) per 100 person-years in trial participants, lower than in the general population with type 1 diabetes. SEARCH reported that the rate of acute complications, emergency department visits, and hospitalizations were lower among youth using insulin pumps compared to all other regimens (175), and no increase in DKA was seen among pump users in the T1D Exchange Clinic Registry (172).

In Europe, large decreases in prevalence of DKA at onset of diabetes over time have been reported from Sweden (176) and Finland (177,178) from the late 1970s to the mid-2000s. These countries had programs directed at increased DKA awareness, which may partially explain the changes, since no such trends were reported from Germany or Austria (179,180,181) over a similar time period. In contrast, limited long-term trend information is available from North America (169), with slightly lower prevalence at onset in 1998–2001 than in 1978–1982. In addition, no significant changes in overall DKA hospitalization rates from 1991 to 1999 were seen in Ontario youth age 0–19 years (182), and an increase was reported in older youth from Nova Scotia (183). Consistent with results from the Pediatric Diabetes Consortium (184), SEARCH reported that the frequency of DKA at onset of type 1 diabetes remained unchanged at ~30% of U.S. youth at onset from 2002–2010, indicating a persistent need for increased awareness and better access to health care (185). In this study, DKA continued to occur at relatively high rates, especially in younger new-onset persons and those who were socially disadvantaged. Interestingly, Elding Larsson *et al*. reported on the DKA prevalence at onset among youth participating in TEDDY in four countries (186). TEDDY closely monitors children at high risk for type 1 diabetes over time, and DKA prevalence at onset was about one-half of that reported in population-based registries in the same countries where TEDDY is conducted (186). Thus, programs of DKA awareness hold promise to reduce the frequency of this complication at diabetes onset.

Type 2 Diabetes. Youth with type 2 diabetes can also present in DKA, with reported frequencies of 8%–29% (16,22,170,187). A lower prevalence (4.2% at age 0–18 years) in First Nation Canadian youth with type 2 diabetes has been reported (23). Youth with type 2 diabetes may also present with hyperglycemic hyperosmolar nonketotic coma (188). SEARCH found that DKA in youth with type 2 diabetes was more frequent in African Americans and Hispanics than in non-Hispanic whites (Table 15.1), consistent with results from other studies (16,22,187). DKA in youth with type 2 diabetes was also associated with lower family income and parental education and less health insurance independent of race/ethnicity (170). Over the time period of 2002–2010, DKA prevalence at onset of type 2 diabetes declined from 11.7% to 5.7% (p for trend=0.005) (176).

Hypoglycemia

Hypoglycemia in large population-based studies is based on report of requiring assistance with low blood sugar, loss of consciousness or seizure, and use of emergency department or hospitalization. Rarely are concurrent blood glucose levels measured.

Type 1 Diabetes. Severe hypoglycemia (usually requiring assistance/medical attention or leading to seizure or coma) occurs in 4%–35% of children with type 1 diabetes each year (Table 15.1) (173,189,190,191). The rate is consistent with that seen in the conventionally treated group in the DCCT (27.8 per 100 person-years) (174) and with that seen in a Denver, Colorado, study (19 per 100 person-years) (173), though it was somewhat higher in Boston, Massachusetts, and Houston, Texas, cohorts (37.6 per 100 person-years) (191). In these latter cohorts, the highest rates were among youth treated primarily with NPH insulin and were lowest among insulin pump users (191). In the U.S. T1D Exchange Clinic Registry, covering 68 tertiary diabetes treatment centers, one or more episodes of hypoglycemia (defined as loss of consciousness or seizure only) in the past year occurred in 5%–10% of subjects (172).

Some differences between studies may be definitional, with higher rates in studies including "requiring assistance" as part of the definition and lower rates in studies based only on loss of consciousness or seizure. In addition, unrecognized hypoglycemia occurs commonly, with up to 73% of hypoglycemic episodes occurring without detection by children or their parents (192). Hypoglycemia unawareness, a condition more common in those with more intensive glycemic control, longer diabetes duration, and younger age of onset, further increases the risk of severe hypoglycemia (190).

Type 2 Diabetes. Systematic reports of population studies of youth with type 2 diabetes and the prevalence or incidence of hypoglycemia have not been published.

MICROVASCULAR COMPLICATIONS

Diabetic Retinopathy

Type 1 Diabetes. While a large number of studies of diabetic retinopathy have been conducted worldwide, few are contemporary studies among younger persons with type 1 diabetes in North America. These studies are summarized in Table 15.2. The pioneering Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) conducted long-term follow-up of persons diagnosed at age ≤30 years starting in 1979 and defined the risk of diabetic retinopathy at 15 (193), 20 (194), and 25 years (195) of diabetes duration. Starting about a decade after WESDR, two

additional studies began: the Wisconsin Diabetes Registry Study (WDRS) (193) and the Pittsburgh Epidemiology of Diabetes Complications (EDC) study (196).

The WDRS followed 474 youth with type 1 diabetes onset at age <14 years and showed that the prevalence of any diabetic retinopathy was 10% at short durations (3–7 years) and 40% with up to 15 years duration (193). Diabetic retinopathy prevalence declined in each age/duration group when comparing the later WDRS to the WESDR (194) in the same geographic area. The authors note that improvements in glycemia with multiple daily insulin injections were at least partially responsible (194). Similarly, the EDC, which followed 906 youth-onset type 1 diabetes participants for up to 30 years, reported a decline in diabetic retinopathy prevalence at 20 years of diabetes duration for cohorts diagnosed in 1975–1980 (26.5%) compared to those diagnosed in 1965–1969 (38%) (196). Similar findings of reduced diabetic retinopathy prevalence in cohorts diagnosed at later times have been reported from Europe (197) and Australia (198,199), after matching on age of onset and diabetes duration. A much higher proportion of youth were on more intensive insulin regimens in later years, which likely contributed to the decline in diabetic retinopathy prevalence (199).

Significant reductions in diabetic retinopathy occurrence and progression were shown in adolescent participants in the intensive insulin therapy group of the landmark DCCT and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study compared to those in the conventional treatment group (174,200,201). The adolescents in the intensive group in the DCCT/EDIC had significant reductions in diabetic retinopathy progression at the end of the DCCT, as well as after 4 years of follow-up in the EDIC (200). However, after 10 years of follow-up in the EDIC (201), the risk differential was reduced among adolescents (32%, p=0.134), whereas it was maintained in adult participants (56%, p<0.0001). In addition, the prevalence of a further three-step progression in EDIC was the same at 10 years of follow-up for adolescents in both treatment groups, while still reduced in adults. In the intensive group, 93% of the observed difference in further diabetic retinopathy progression between adolescents and adults was explained by the mean A1c differences (higher in adolescents) in the DCCT time period. This finding indicates that lower A1c during the intensive time period is an important determinant of the long-term durability of its benefits. Thus, early and sustained glycemic control is crucial in reducing diabetic retinopathy progression among youth with type 1 diabetes. The 18-year DCCT follow-up now shows that the cumulative incidence of multiple retinopathy outcomes remains lower in the intensively treated group; however, the year-to-year incidence is now similar between the two groups, owing in large part to a reduction in risk in the former conventional treatment group (202).

Given the "metabolic memory" of lower A1c resulting in reduced retinopathy (and other microvascular complications) several years later, the long-term retinopathy risks identified in multiple studies of older cohorts are not likely to be good estimates of the risk of retinopathy for later cohorts that have undergone better glycemic control than previously. Nonetheless, substantial proportions of current youth have poor glycemic control (203), and their risk may approximate that from older cohorts. Indeed, a SEARCH pilot and feasibility study reported a 17% prevalence of diabetic retinopathy in 222 multiethnic youth with type 1 diabetes and average duration of only 6.8 years (204). Racial/ethnic disparities in screening for diabetic retinopathy have been reported, with whites and those with better glucose control being more likely to be screened than African Americans or Hispanics seen at a single diabetes treatment center in Philadelphia (205).

Type 2 Diabetes. The literature on diabetic retinopathy among youth with type 2 diabetes is more limited. Available data are summarized in Table 15.2. Among Pima Indians, youth with type 2 diabetes onset at age <20 years had an incidence rate of 9.7 per 1,000 person-years after 5–10 years of duration; however, rates were 60% lower at every duration than those in persons with later onset of diabetes at age 40–59 years (206). A small study from New York City of 40 (largely minority) youth with type 2 diabetes found a prevalence of 2.5% of any diabetic retinopathy after an average duration of 22 months (207). The SEARCH pilot study (204) of 43 youth with type 2 diabetes and duration of 7.2 years found 42% with any diabetic retinopathy, including one person with proliferative retinopathy. Minority youth with type 2 diabetes had more diabetic retinopathy than non-Hispanic whites (204). Dart *et al*. linked clinical and health care administrative data in Manitoba, Canada, and found that youth with type 2 diabetes had similar prevalence of retinopathy (11.7%) to those with type 1 diabetes (13.8%), though there was a trend toward higher rates among type 2 diabetic youth after 15 years (208).

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) was a randomized clinical trial of youth age 10–17 years with a mean type 2 diabetes duration of 7.8 months at trial start who had A1c ≤8.0% (≤64 mmol/mol) on metformin therapy, a BMI ≥85th percentile, and controlled blood pressure and creatinine clearance >70 mL/min (209). They compared metformin alone versus metformin plus a lifestyle intervention versus metformin plus rosiglitazone to prevent loss of glycemic control as the primary outcome. Retinal photographs were taken in the last year of the trial when mean duration was 4.9 years and showed that the prevalence of any diabetic retinopathy was 13.7%, reaching 25.0% in those with A1c >7.0% (>53 mmol/mol) (210). The differences between the SEARCH (population-based study) and TODAY (clinical trial) are likely due to longer duration and poorer control in SEARCH participants.

Outside of North America, in an Australian cohort, prevalence of diabetic retinopathy among youth with type 2 diabetes was 4% after 1.3 years of duration; however, only 25 youth with type 2

TABLE 15.2. Retinopathy Among Persons With Youth-Onset Diabetes

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
Type 1 diabetes				
193	WESDR baseline examination; 521 T1 persons with age of onset <30 years; 1979–1980	Seven-field stereo photographs	Prevalence of any retinopathy by diabetes duration (years) and exam age (years) Duration: 3–7 / 8–11 / 12–15 Exam age 10–14: 8% / 50% / NA Exam age 15–19: 48% / 78% / 91% Exam age 20–40: 53% / 82% / 95%	Population-based
193	WDRS, 474 T1 youth with age of onset ≤30 years; ≤14-year follow-up; 1987–1992	Seven-field stereo photographs	Prevalence of any retinopathy by diabetes duration (years) and exam age (years) Duration: 3–7 / 8–11 / 12–15 Exam age 10–14: 10% / 32% / 40% Exam age 15–19: 21% / 48% / 62% Exam age 20–40: 27% / 58% / 82%	Population-based; prevalence lower than the WESDR study reported in same paper from Wisconsin, above.
196	EDC (Pittsburgh, PA); 906 T1 persons with age of onset <18 years; onset 1965–1980; baseline 1986–1988; mean age at baseline 28 years; mean diabetes duration 19 years; follow-up through 2000	Three-field stereo photos or laser photocoagulation if no photo	Cumulative incidence of proliferative retinopathy by diabetes duration (years) and period of diabetes diagnosis Duration: 20 / 25 Period of diagnosis 1965–1969: 38.0% / 55.0% Period of diagnosis 1970–1974: 35.0% / 51.0% Period of diagnosis 1975–1980: 26.5% / NA	70% participated.
195	WESDR, 25-year follow-up; 955 T1 persons with age of onset <30 years; baseline 1980–1982	Seven-field stereo photographs	Prevalence of any retinopathy by diabetes duration (years) and period of diabetes diagnosis Duration: 10–14 / 20–24 / 30–34 Period of diagnosis 1922–1969: 19% / 45% / 58% Period of diagnosis 1970–1974: 10% / 41% / 50% Period of diagnosis 1975–1980: 9% / 24% / 40%	Population-based; declining prevalence of proliferative diabetic retinopathy in later periods of diagnosis (from 1922 to 1980).
194	Comparison of WDRS (N=305) and WESDR (N=583) at 20 years diabetes duration, by severity of retinopathy; T1 persons with age of onset ≤30 years	Seven-field stereo photographs; severity based on WESDR scale	Prevalence of retinopathy by study cohort and severity WDRS / WESDR Any: 92.1% / 97.2% None: 79% / 2.7% Nonproliferative: 81.6% / 64.3% Proliferative (and treated): 10.5% / 35.7%	Population-based; WDRS began in 1987–1992; WESDR began in 1979–1980.
204	SEARCH, pilot study; convenience sample of 222 T1 youth with age of onset <20 years; mean diabetes duration 6.8 years; 2009–2010	45° non-mydriatic camera photos (two per eye) with central reading	Prevalence of any retinopathy: 17.0%	Not population-based; crude prevalence was lower in non-Hispanic whites than minorities.
248	Sydney Australia, Royal Prince Alfred Hospital clinical cohort; 470 T1 persons with age of onset 15–30 years; mean age of onset 25.1 years; mean diabetes duration 14.7 years; 1986–2011	Clinical fundoscopy and later retinal photography	Prevalence of any retinopathy: 41.0%	Not population-based; serves large geographic region of Sydney, Australia; A1c mean 8.1%.
Type 2 diabetes				
206	Pima Indians, AZ; dynamic cohort follow-up from 1965; 178 T2 youth with age of onset <20 years; 971 T2 adults age 40–59 years at onset as comparison	Dilated direct ophthalmoscopy	Incidence of any retinopathy per 1,000 by diabetes duration (years) and age (years) of onset Duration: 5–10 / 10–15 / 15–20 Age <20: 9.7 / 42.3 / 68.7 Age 40–59: 35.1 / 85.6 / 99.1	Population-based; youth-onset persons had lower retinopathy incidence (hazard ratio 0.42) not explained by adjustment for risk factors.
207	New York City, NY, tertiary referral center; 40 T2 youth with age of onset <21 years; average diabetes duration 22 months; largely African American and Hispanic; 2001–2003	Dilated direct and indirect fundoscopy	Prevalence of any retinopathy: 2.5%	Clinic-based; no photography

Table 15.2 continues on the next page.

TABLE 15.2. (continued)

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
204	SEARCH, pilot study; convenience sample of 43 T2 youth; duration ≥5 years; mean age 21.1 years; mean diabetes duration 7.2 years; 2009–2010	45° non-mydriatic camera photos (two per eye) with central reading	Prevalence of any retinopathy 42.0%	Not population-based; crude prevalence was lower in non-Hispanic whites than minorities.
210	TODAY randomized clinical trial in 15 U.S. centers; 517 of 699 T2 youth age 10–17 years; mean diabetes duration 8 months; 2004–2011	Dilated seven standard field retinal photos with central reading	Prevalence of any retinopathy 13.7%	Not population-based; older age, longer diabetes duration, and higher mean A1c all associated with higher prevalence; youth with BMI >37.8 kg/m^2 had lower prevalence: 9.3% vs. ~16%.
248	Sydney Australia, Royal Prince Alfred Hospital clinical cohort; 354 T2 persons with age of onset 15–30 years; mean age of onset 25.6 years; mean diabetes duration 11.6 years; 1986–2011	Clinical fundoscopy and later retinal photography	Prevalence of any retinopathy 37.0%	Not population-based; serves large geographic region of Sydney, Australia; A1c mean 8.1%.
208	Manitoba tertiary referral hospital; 342 T2 youth; 1,011 T1 youth; 1,710 nondiabetic controls; 1986–2007	Manitoba health insurance records for clinically diagnosed retinopathy (ICD codes)	Prevalence at end of follow-up T2 ..... 11.7%* T1..... 13.8%* Control ..... 0.8% * p=nonsignificant	Not population-based; however, clinic cares for 86% of all diabetic youth in province.

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; BMI, body mass index; EDC, Epidemiology of Diabetes Complications study; HR, hazard ratio; ICD, International Classification of Diseases; NA, not applicable; SEARCH, SEARCH for Diabetes in Youth study; T1, type 1 diabetes; T2, type 2 diabetes; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth (trial); WDRS, Wisconsin Diabetes Registry Study; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

SOURCE: References are listed within the table.

diabetes were evaluated (211). A report from New Zealand pediatric clinical centers found the prevalence of diabetic retinopathy from chart review to be 8% after 3 years of duration (212). Among 15 youth with type 2 diabetes (mean duration 2.1 years), no retinopathy was detected; however, several abnormalities (focal retinal neuropathy, retinal thinning, and venular dilation) were detected that were absent among nondiabetic control youth (213).

Nephropathy

The spectrum of diabetic renal disease typically starts with low levels of detectable albumin in the urine ("microalbuminuria," usually 20–200 µg/min albumin excretion rate [AER] or albumin:creatinine ratio [ACR] ≥30 µg/mg or ≥3 mg/mmol), progresses through macroalbuminuria (usually ≥200 µg/min AER or >300 mg/24 hours) to renal insufficiency (marked by falling glomerular filtration rates and/or rising serum creatinine levels) and end-stage renal disease (ESRD) requiring dialysis or renal transplant (214). A subset (15%–20%) of persons with diabetes and renal failure do not progress through a proteinuria phase (non-proteinuric [normoalbuminuric] diabetic nephropathy) (215,216,217). Among youth, the later stages of renal insufficiency and ESRD are rare, and the early natural history of microalbuminuria and macroalbuminuria is usually followed. Studies of nephropathy in North American youth are summarized in Table 15.3.

Type 1 Diabetes. The T1D Exchange Clinic Registry reported a prevalence of microalbuminuria diagnosis (clinical diagnosis of sustained elevation and either most recent ACR ≥30 mg/g or treatment with an angiotensin-converting enzyme [ACE] inhibitor or angiotensin II receptor blocker [ARB]) of 4.4% among youth age <20 years with ≥1 year of duration (218). This prevalence is similar to another large clinic-based registry in Germany (219). The T1D Exchange Clinic Registry found that longer duration of diabetes, higher mean A1c level, older age, female sex, higher diastolic blood pressure, and lower BMI were also significantly associated with a diagnosis of microalbuminuria. SEARCH reported that the prevalence of a single elevated ACR after only 3.7 years of diabetes duration was 9.2% in almost 3,000 youth with type 1 diabetes (220), higher than that seen in the T1D Exchange Clinic Registry. This result may have been due to use of a single elevated ACR, rather than a sustained level as required by the T1D Exchange Clinic Registry, or a demographically dissimilar study group, including different proportions of youth with longer duration, older age, or worse glycemic control. After approximately 6 years of duration, Dart *et al.* reported a prevalence of microalbuminuria among Manitoba youth with type 1 diabetes of 12.7%, with 1.6% having macroalbuminuria and 1.4% already in renal failure (221). In a follow-up study linking clinical data to Manitoba electronic health records for a 25-year follow-up, they found that 2.3% of type 2 diabetic youth had used dialysis compared with none of the type 1 diabetic youth, and 8.9% had electronic health record evidence of any renal complication versus 2.7% of youth with type 1 diabetes and 0.6% of 1,700 nondiabetic youth (208). These estimates are consistent with those reported by the WESDR in patients

TABLE 15.3. Nephropathy Among Persons With Youth-Onset Diabetes

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
Type 1 diabetes				
223	EURODIAB: 1,215 T1 youth with age of onset <36 years; 31 clinic sites; mean diabetes duration 18 years; 1988–1990 EDC (Pittsburgh, PA): 627 T1 youth with age of onset <17 years; mean diabetes duration 20 years; 1986–1998	EURODIAB: one 24-hour urine EDC: two of three timed urine AER microalbuminuria 20–200 µg/min; macroalbuminuria >200 µg/min	Prevalence EURODIAB Microalbuminuria ..... 25% Macroalbuminuria ..... 12% EDC Microalbuminuria ..... 22% Macroalbuminuria 27%	Large clinic-based series; differences in macroalbuminuria were not explained by hypertension, glycemic control, smoking, diabetes duration, or age.
222	WESDR; 10 years follow-up of 756 T1 youth with age of onset <30 years; 1984–1996	Serum creatinine ≥2 mg/dL, dialysis, or transplant	10-year cumulative incidence of renal insufficiency Male ..... 17.4% Female ..... 11.1% Diabetes duration (years) 0–9 ..... 5.6% 10–14 ..... 15.2% 15–19 ..... 18.9% 20–24 ..... 18.3% 25–29 ..... 12.5% 30–34 ..... 11.1% ≥35 ..... 33.5%	Population-based; age, A1c, hypertension, and proteinuria were all risk factors for outcome.
358	Allegheny County, PA, Registry; follow-up of 798 T1 persons with age of onset <18 years; average diabetes duration 25 years; through 1999	Self-reported dialysis or transplant	Cumulative incidence of ESRD (life table) at 20 years diabetes duration by diagnosis years 1965–1969 ..... 9.1% 1970–1974 ..... 4.7% 1975–1979 ..... 3.6%	Population-based; ascertained 90.7% for vital status and 74.2% for ESRD; higher ESRD cumulative incidence in blacks vs. whites.
220	SEARCH, six U.S. centers; 2,885 T1 youth with age of onset <20 years; mean diabetes duration 3.7 years; 2001–2003	ACR ≥30 µg/mg	Prevalence of elevated ACR 9.2%	Population-based; no difference by race/ethnicity.
359	EDC (Pittsburgh, PA) cohort of 933 T1 persons with age of onset <17 years; mean diabetes duration of 19 years; mean 18-year follow-up; 1986–1996	Timed urine AER Macroalbuminuria: >200 µg/min (>300 mg /24 hours) in two of three samples ESRD: dialysis or transplant	Cumulative incidence per 1,000 person-years by sex, diabetes duration, and diagnosis cohort Macroalbuminuria — Men / Women 25 years duration 1950–1964 ..... 30.1 / 18.0 1965–1980 ..... 34.4 / 38.0 30 years duration 1950–1964 ..... 56.5 / 32.9 1965–1980 ..... 46.2 / 45.1 ESRD 25 years duration 1950–1964 ..... 30.6 / 18.0 1965–1980 ..... 7.6 / 13.8 30 years duration 1950–1964 ..... 43.4 / 24.6 1965–1980 ..... 13.7 / 21.0	Marked reduction in ESRD incidence in men in later cohort, less so for women; risk factors explained some of cohort effect in men, not in women. Little difference in macroalbuminuria over time.
221	Manitoba, Canada, tertiary referral center; 1,011 prevalent T1 youth age 1–18 years; mean diabetes duration 6.3 years; 1,710 controls; 1986–2007	Insurance plan records, ICD codes, prescriptions for ESRD, renal failure, any renal complication; clinical laboratory data from center ACR: two of three tests, ≥3 mg/mmol or AER ≥30 mg/24 hour	Prevalence Microalbuminuria ..... 12.7% Macroalbuminuria ..... 1.6% Renal failure ..... 1.4% ESRD 0%	Clinic-based
248	Sydney, Australia, Royal Prince Alfred Hospital clinical cohort; 470 T1 with onset from age 15–30 years; mean age of onset 25.1 years; mean diabetes duration 14.7 years; 1986–2011	ACR >2.5 mg/mmol (males), >3.5 (females) Albuminuria >30 mg/L if no creatinine	Albuminuria prevalence 15.3%	Not population-based; serves large geographic region of Sydney, Australia; A1c mean 8.1%.

Table 15.3 continues on the next page.

TABLE 15.3. (continued)

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
218	T1D Exchange Clinic Registry, 67 U.S.-based pediatric and adult endocrinology practices; 7,549 T1 youth with onset <20 years; diabetes duration ≥1 year; mean age 13.8 years; mean diabetes duration 6.5 years; 2010–2012	Clinical diagnosis of persistent microalbuminuria and last ACR ≥30 mg/g or treatment with ACE or ARB	Prevalence of diagnosis of microalbuminuria ... 4.4%	Not population-based; longer duration of diabetes, higher mean A1c level, older age, female sex, higher diastolic blood pressure, and lower BMI were significantly associated with a diagnosis; 64% with diagnosis were not treated with an ACE or ARB.
Type 2 diabetes				
230	Pima Indians, AZ; 36 T2 youth with age of onset 15–19 years; followed up to 10 years	ACR on spot urine; elevated ACR ≥30 mg/g Macroalbuminuria: ≥0.5 g/g	Microalbuminuria prevalence At diagnosis ... 22% 10 years duration ... 60% Macroalbuminuria At diagnosis ... 0% 10 years duration ... 17%	Population-based
231	Pima Indians, AZ; offspring of diabetic pregnancy (N=50), prediabetic pregnancy (N=246), or normal pregnancy (N=207) in cross-sectional exam for urinary albumin; 1965–1995	Spot urine for albumin and protein; elevated ACR ≥30 mg/g creatinine	Elevated ACR by pregnancy type Diabetic ... 58.0% Prediabetic ... 42.7% Normal ... 40.1%	Population-based; odds ratio 3.8 for elevated ACR in offspring of diabetic vs. prediabetic or nondiabetic mothers
206	Pima Indians, AZ; dynamic cohort follow-up from 1965; 178 T2 youth with age of onset <20 years; 971 T2 adults with age of onset 40–59 years as comparison	Spot urine protein: creatinine ratio ≥0.5 (g protein/g creatinine)	Incidence of nephropathy per 1,000 by diabetes duration (years) and age (years) of onset Duration: 5–10 / 10–15 / 15–20 <20 ... 13.9 / 51.8 / 90.1 40–59 ... 18.8 / 43.2 / 94.3	Population-based; youth-onset had similar rate of nephropathy incidence (adjusted HR 1.2, p=0.38) but lower incidence of retinopathy compared to older-onset persons.
360	New York City, NY, tertiary referral clinic; 26 T2 youth with age of onset 10–18 years; <3 years diabetes duration; antibody-negative; 2004	One 24-hour urine; microalbuminuria: albumin ≥30 mg/day	Prevalence of microalbuminuria T2 youth ... 40.0% Controls ... 0.0%	Clinic-based; blood pressure measures higher in T2 youth with microalbuminuria than those without.
232	Pima Indians, AZ; dynamic cohort follow-up from 1965; 96 T2 youth with age of onset <20 years and age 25–55 years at exam; followed for ESRD to 2002	Dialysis, transplant, or death from diabetic nephropathy	Incidence of ESRD per 1,000 person-years Youth-onset ... 25.0 Adult-onset ... 5.4	Higher rates in youth-onset persons at same age as older-onset persons with diabetes due largely to longer duration of diabetes at same age.
207	New York City, NY, tertiary referral center; 40 T2 youth with age of onset <21 years; largely African American and Hispanic; average diabetes duration 22 months; 2001–2003	Two consecutive spot urines >30 µg albumin/mg creatinine	Prevalence of microalbuminuria ... 27.3%	Clinic-based
220	SEARCH, six U.S. centers; 374 T2 youth with age of onset <20 years; mean diabetes duration 1.9 years; 2001–2003	ACR ≥30 µg/mg	Prevalence of elevated ACR ... 22.2%	Population-based; adjustment for insulin resistance-related variables did not completely explain higher prevalence in T2 vs. T1 youth.
230	Manitoba, Canada, tertiary referral center; 90 T2 youth age 10–19 years; mean diabetes duration 2.5 years; cases prior to 2003	Chart review of clinical testing; ACR on timed urines Microalbuminuria: 3–28 mg/mmol (26.5–247.5 mg/g) Macroalbuminuria: ≥28 mg/mmol (≥247.5 mg/g)	Prevalence At diagnosis ... 29% Any one positive ... 53% Persistent macroalbuminuria ... 16%	98% First Nation or Métis youth

Table 15.3 continues on the next page.

TABLE 15.3. (continued)

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
233	Pima Indians, AZ; dynamic cohort follow-up from 1965; 1,850 T2 persons age 5–45 years; followed until 2007	Dialysis, transplant, or death from diabetic nephropathy	Cumulative incidence of ESRD at age 45 years by presence of diabetes in pregnancy Yes ..... 19.3% No 5.1%	Fourfold higher risk of ESRD among persons born of diabetic pregnancy; explained by longer duration of diabetes to age 45 years.
234	Pima Indians, AZ; dynamic cohort follow-up; 3,597 NGT, 259 IGT, 103 T2 youth age of onset 5–19 years followed until 2007; mean follow-up 25.2 years; 1982–2007	Elevated ACR Microalbuminuria: ≥30–<300 mg/g creatinine Macroalbuminuria: ≥300 mg/g	Prevalence of elevated ACR at baseline T2 ..... 21.4% IGT ..... 6.6% NGT ..... 7.2% Incidence of progression per 1,000 person-years Type 2 diabetes Normal to macroalbuminuria ..... 23.7 Micro- to macroalbuminuria ..... 60.0 No diabetes Normal to macroalbuminuria ..... 1.3 Micro- to macroalbuminuria 5.5	Population-based; among those with albuminuria on first measurement, 75.4% of nondiabetic persons regressed, whereas only 27.3% of T2 persons regressed.
221	Manitoba, Canada, tertiary referral center; 342 prevalent T2 youth age 1–18 years; mean diabetes duration 1.6 years: 1,710 nondiabetic controls; 1986–2007	Insurance plan records, ICD codes, prescriptions for ESRD, renal failure, any renal complication; clinical laboratory data from center ACR: two of three tests, ≥3 mg/mmol or AER ≥30 mg/24 hours Macroalbuminuria: ACR >28 mg/mmol or >300 mg albumin/24 hours	Prevalence Microalbuminuria ..... 26.9% Macroalbuminuria ..... 4.7% Renal complications ..... 8.9% Renal failure ..... 6.7% ESRD 2.3%	Mean age of microalbuminuria: T2 youth 14.9 years; T2 youth had HR 4.03 vs. T1 youth for renal failure; T2 vs. controls: HR 23.8 for renal failure, HR 39.1 for ESRD; 50% of T2 youth were Oji-Cree.
235	TODAY randomized clinical trial in 15 U.S. centers; 699 T2 youth age 10–17 years at trial entry; mean diabetes duration 8 months; 2004–2011	Microalbuminuria: two of three ACR ≥30 µg/mg in 3 months	Prevalence of microalbuminuria Baseline ..... 6.3% Trial end 16.6%	Not population-based. Mean follow-up to trial end: 3.9 years
248	Sydney, Australia, Royal Prince Alfred Hospital clinical cohort; 354 T2 youth with age of onset 15–30 years; mean age of onset 25.6 years; mean diabetes duration 11.6 years; 1986–2011	ACR >2.5 mg/mmol (males), >3.5 (females) Albuminuria >30 mg/L if no creatinine	ACR at final visit ..... 2.2 Albuminuria prevalence 47.4%	Not population-based; serves large geographic region of Sydney, Australia; A1c mean 8.1%; ACR and albuminuria significantly higher than T1 (p<0.0001).
208	Manitoba tertiary referral hospital; 342 T2 youth; 1,011 T1 youth; 1,710 nondiabetic controls; 1986–2007	Manitoba health insurance records for clinically diagnosed renal complication, failure, or dialysis (ICD)	Prevalence at end of follow-up T2 / T1 / Control Renal complication ..... 8.9% / 2.7% / 0.6% Renal failure ..... 6.7% / 1.4% / * Dialysis ..... 2.3% / 0.0% / * * Data suppressed	Not population-based; however, cares for 86% for all diabetic youth in province. Life table shows significantly shorter renal survival in T2 vs. T1 (p<0.0001).

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; ACE, angiotensin-converting enzyme inhibitor; ACR, albumin:creatinine ratio; AER, albumin excretion rate; ARB, angiotensin II receptor blocker; BMI, body mass index; EDC, Epidemiology of Diabetes Complications study; ESRD, end-stage renal disease; HR, hazard ratio; ICD, International Classification of Diseases; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; SEARCH, SEARCH for Diabetes in Youth study; T1, type 1 diabetes; T2, type 2 diabetes; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

SOURCE: References are listed within the table.

diagnosed at age <30 years; the cumulative incidence of microalbuminuria rose from 5.6% among those with 0–9 years of diabetes duration to 15.2% for 10–14 years, then stabilized until ≥35 years, when the cumulative incidence was 33.5% (222). Similarly, in the Pittsburgh EDC study (223), at average diabetes duration of 20 years, the prevalence was 22% for microalbuminuria and 27% for macroalbuminuria (223). There was little difference in macroalbuminuria incidence by year of diagnosis. Interestingly, in the large, multicenter EURODIAB complications study, the prevalence of macroalbuminuria was about one-half that of the levels seen in Pittsburgh and was not explained by differences in factors known to influence albuminuria (hypertension, treatment, A1c, age, diabetes duration, smoking, sex) (223).

In contrast to the inexorable progression of nephropathy from microalbuminuria to overt proteinuria, studies have shown that regression of microalbuminuria occurs frequently. In adults with youth-onset

type 1 diabetes, Perkins *et al.* showed that the 6-year cumulative incidence of regression of microalbuminuria (defined as a 50% reduction in urinary albumin excretion from one 2-year period to the next) was 58% (224). Similarly, in youth with type 1 diabetes (mean duration 7.6 years and mean age approximately 15 years), the 10-year cumulative incidence of regression was 47.6% (225). Since microalbuminuria is associated with insulin resistance (226) and predicts not only nephropathy, but also macrovascular events and total mortality (227), it may not be surprising that fluctuations and regression would be associated with improved levels of glycemia and cardiovascular risk factors. Lowering of A1c by more intensive insulin treatment has been rigorously shown to reduce nephropathy by the DCCT/EDIC study (228). Among the adolescents at the end of the DCCT, there was a 10% relative risk reduction (RRR) for nephropathy in the primary prevention cohort (diabetes duration <6 years, AER <40 mg/24 hours) (174) and a 55% RRR in the secondary prevention cohort (duration 1–15 years, AER <200 mg/24 hours) (174). Four years after the end of the DCCT during the EDIC follow-up (200), among those free of microalbuminuria at DCCT closeout, the RRR was 48% for development of microalbuminuria and 85% for the development of macroalbuminuria (200). Thus, for youth and young adults, improved glycemic control early in the natural history of type 1 diabetes reduces the development of both microalbuminuria and macroalbuminuria.

Type 2 Diabetes. The prevalence of microalbuminuria at diabetes diagnosis among Pima Indians with youth-onset type 2 diabetes was 22% (229), similar to estimates seen in other North American studies at diagnosis or within 1–2 years (Table 15.3) (207,220,221). Among multiethnic U.S. youth, the prevalence of elevated ACR among youth with type 2 diabetes was 22.2%, significantly higher than among type 1 diabetic youth (9.2%), and was higher among minorities than non-Hispanic whites (220). Female sex, higher A1c and triglyceride values, and elevated blood pressure, in addition to type of diabetes, were independently associated with elevated ACR (220). Among First Nation or Métis youth in Manitoba, Canada, the prevalence of microalbuminuria was high (53% at 2.5 years of duration), and macroalbuminuria occurred in 16% of youth with type 2 diabetes (230).

A series of elegant studies have largely defined the natural history of diabetic nephropathy in youth with type 2 diabetes among the Pima Indians (206,229,231,232,233,234). The prevalence of elevated albuminuria was higher in Pima Indian youth with diabetes than in those without it (234). Among youth without diabetes, albuminuria was largely transient, whereas for those with type 2 diabetes, it was more likely to be persistent and to significantly predict progression to persistent macroalbuminuria (234). Incidence rates of proteinuria were compared at similar follow-up durations among Pima with youth-onset (age <20 years) type 2 diabetes and Pima with onset at age 40–59 years (206). At each duration, no significant differences in the incidence rates of proteinuria were found between younger and older onset individuals (206), showing that duration is the major determinant of renal disease regardless of age of onset. However, by the attained age of 45 years, 19.3% of youth-onset diabetes Pima had ESRD compared to only 5% of adult-onset diabetes persons, due to the longer duration of diabetes among those with young onset (233). This suggests with the increasing trend of early-onset type 2 diabetes, a greater burden of dialysis and transplant will occur in the thirties to fifties, instead of two decades later, thereby further reducing life expectancy and increasing diabetes costs.

Only two studies of nephropathy in North American youth with type 2 diabetes other than in the Pima Indians have been conducted. Dart *et al.* reported that among 342 youth with type 2 diabetes seen in Manitoba, 6.7% already had renal failure over a mean follow-up of 5.3 years (221). Among those with persistent albuminuria, 9.1% developed renal failure compared to only 1.1% among those without albuminuria. They also followed a cohort of youth with type 1 diabetes and found that compared with youth with type 1 diabetes, those with type 2 diabetes had a fourfold increased risk of developing renal failure, adjusted for age at diagnosis, A1c, BMI z-score, and year of diagnosis (221). The TODAY trial reported that microalbuminuria was present in 6.3% at randomization and rose to 16.6% after a mean follow-up of 3.9 years; it was higher in those with higher A1c, but not different by treatment arm, sex, or race/ethnicity (235). A positive result for microalbuminuria required two of three ACRs ≥30 μg/mg to be positive over a minimum of 3 months—criteria rarely used in observational studies. Thus, studies using only a single ACR will likely show higher prevalence.

Taken together, these data suggest that the risk of nephropathy is substantially higher in youth with type 2 diabetes versus type 1 diabetes at similar duration. Similar findings were reported by studies outside North America. Japanese and Korean youth with type 2 diabetes onset at age <30 years had almost twice the prevalence of proteinuria at each duration of follow-up compared with type 1 diabetic youth (236). In a study in New South Wales, Australia, the prevalence of microalbuminuria was 28% in type 2 diabetic and 6% in type 1 diabetic youth (211). How much of these differences by type of diabetes can be explained by differences in known risk factors remains to be elucidated. Some of the differences may be explained by cardiovascular, inflammatory, and insulin resistance related factors (220), which have not been explored in most studies.

One known risk factor for diabetic nephropathy is exposure to maternal diabetes *in utero*. Among the Pima Indians, offspring of mothers who were diabetic during pregnancy had significantly higher rates of proteinuria (231) and ESRD (233) many years later than offspring of normal or prediabetic mothers. Among Manitoba youth with type 2 diabetes, 16% had mothers with pregestational diabetes compared with only 2.7% of youth with type 1 diabetes (221). Thus, maternal diabetes may be responsible not only for

increasing the risk of type 2 diabetes in youth, but also for the increased risk of nephropathy in youth with type 2 diabetes due to the earlier onset of diabetes in those with *in utero* exposure.

Neuropathy

The topic of diabetic neuropathies is complex due to the diverse clinical manifestations and to difficulties in measurement methods (237,238). This section focuses on chronic distal symmetric polyneuropathy (i.e., diabetic peripheral neuropathy [DPN]) and cardiac autonomic neuropathy (CAN) in youth with type 1 and type 2 diabetes. Data on neuropathy in North American youth are summarized in Table 15.4.

Diabetic Peripheral Neuropathy. DPN is usually diagnosed using a history of altered sensation in the feet (e.g., burning, tingling, numbness) and a clinical examination that includes altered pain and light touch sensation, decreased vibration detection in the foot (either a tuning fork or calibrated vibration tester), and decreased deep tendon reflexes at ankle and/or knee. The examination includes a Semmes-Weinstein 10 g monofilament for standardized light touch and a standardized symptoms questionnaire and grading (239).

Type 1 Diabetes. The limited information available on the prevalence of DPN among youth with type 1 diabetes in North America is shown in Table 15.4. Studies are difficult to summarize due to substantial differences in measurement methods; however, it is clear that abnormalities are prevalent after relatively short diabetes duration (6–8 years), if methods are sensitive (240,241). Nelson *et al*. found an abnormal peripheral clinical exam among 36% of type 1 diabetic youth at a mean age of only 14 years with mean duration of 8 years (241). Among Pittsburgh youth with duration of type 1 diabetes <10 years, no DPN was found using the fairly stringent clinical (DCCT) definition, but with increased duration, the prevalence of DPN reached 58% in those age ≥30 years (242). DPN prevalence was associated with higher A1c level, lower high-density lipoprotein (HDL) cholesterol, and smoking. In the long-term follow-up of this cohort, a decreasing prevalence of DPN among persons diagnosed in later cohorts has been shown (196).

In contrast to North America, numerous large clinic- and population-based studies of DPN have been conducted in Europe. The EURODIAB IDDM Complications Study reported a baseline prevalence of DPN of 28% at a mean diabetes duration of 15 years among persons with type 1 diabetes age of onset <36 years and subsequently reported a cumulative incidence of 23.5% over 7 years of follow-up in those free of neuropathy at baseline. A similar DIAMOND DIACOMP study of youth with type 1 diabetes age of onset <15 years and a mean duration of 13 years found 5.3% prevalence on exam at age 5–14 years and 28.9% at age 15–24 years (243). Studies in Australia found a prevalence of abnormal thermal and vibration tests in 16% after only 4 years of duration, though most were not symptomatic (244). Eppens *et al*. found a DPN prevalence of 27% after a median duration of 6.8 years, using thermal and

TABLE 15.4. Neuropathy Among Persons With Youth-Onset Diabetes

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
PERIPHERAL NEUROPATHY				
Type 1 diabetes				
242	EDC (Pittsburgh, PA); 400 T1 youth with age of onset <17 years, on insulin at discharge; mean diabetes duration 19.9 years; 1986–2003	Clinical history and exam; abnormal: ≥2 symptoms, sensory/ motor signs, and/or absent reflexes	Prevalence of peripheral neuropathy by age (years) at exam <18 ..... 3% 18–29 ..... 18% ≥30 ..... 58%	Hospital-based but representative of Allegheny County registry; no sex difference; duration, A1c, HDL cholesterol, and smoking were significantly associated in adjusted analysis; no neuropathy at <10 years duration.
196	EDC (Pittsburgh, PA); 906 T1 youth with age of onset <18 years; onset 1965–1980; baseline 1986–1988; mean age at baseline 28 years; mean diabetes duration 19 years; follow-up through 2000	≥2 symptoms and/or reduced/absent reflexes and abnormal vibratory threshold (DCCT definition)	Cumulative incidence of confirmed distal symmetric neuropathy by diabetes duration (years) and period of diabetes diagnosis Duration: 20 / 25 Period of diagnosis 1965–1969 ..... 34.0% / 49.0% 1970–1974 ..... 20.5% / 36.0% 1975–1980 ..... 19.0% / NA	70% participated; significant decline across diagnosis year cohorts.
241	Calgary, Alberta, Canada; 73 T1 youth; mean age 13.7 years; mean diabetes duration 8.1 years	Clinical exam; nerve conduction velocities (NCV); vibration perception threshold (VPT); tactile perception threshold (three filaments) (TPT)	Prevalence Abnormal exam ..... 36% Reduced NCV ..... 57% Abnormal VPT ..... 51% Abnormal TPT 26%	Clinic-based, 22% of 339 eligible; similar characteristics in non-participants; most asymptomatic

Table 15.4 continues on the next page.

TABLE 15.4. (continued)

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
240	SEARCH, five U.S. centers; pilot sample, 347 T1 youth; mean age 15.6 years; mean diabetes duration 6.2 years; 2010	MNSI exam (positive: >2 components)	Prevalence of peripheral neuropathy 8.2%	Pilot sample of population-based study
248	Sydney, Australia, Royal Prince Alfred Hospital clinical cohort; 470 T1 with age of onset 15–30 years; mean age of onset 25.1 years; mean diabetes duration 14.7 years; 1986–2011	VPT by biothesiometer; Z score adjusted for age	VPT score at final visit.....1.8	Not population-based; serves large geographic region of Sydney, Australia; A1c mean 8.1%; VPT score significantly lower than T2 (p<0.0001).
Type 2 diabetes				
240	SEARCH, five U.S. centers; pilot sample, 71 T2 youth; mean age 21.6 years; mean diabetes duration 7.6 years; 2011	MNSI exam (positive: >2 components)	Prevalence of peripheral neuropathy 26.0%	Pilot sample of population-based study
248	Sydney, Australia, Royal Prince Alfred Hospital clinical cohort; 354 T2 with age of onset 15–30 years; mean diabetes duration 11.6 years; mean age of onset 25.6 years; 1986–2011	VPT by biothesiometer; Z score adjusted for age	VPT score at final visit.....2.3	Not population-based; serves large geographic region of Sydney, Australia; A1c mean 8.1%; VPT score significantly higher than T1 (p<0.0001).
208	Manitoba tertiary referral hospital; 342 T2 youth; 1,011 T1 youth; 1,710 nondiabetic controls; 1986–2007	Manitoba health insurance records for clinically diagnosed neuropathy (ICD codes)	Prevalence at end of follow-up T2 ..... 7.6% T1.....5.0% Control 3.6%	Not population-based; however, cares for 86% for all diabetic youth in province. Life table shows significantly shorter neuropathy-free survival in T2 vs. T1 (p<0.001).
CARDIAC AUTONOMIC NEUROPATHY				
Type 1 diabetes				
255	EDC (Pittsburgh, PA); 168 T1 youth with age of onset <17 years, on insulin at discharge; mean age 29.4 years; mean diabetes duration 20.5 years; 1986–1988	Office-based methods: expiration/inspiration (E:I) ratio	Prevalence of abnormal E:I ratio 37.5%	Hospital-based but representative of Allegheny County registry; multivariate: females, LDL and HDL cholesterol, and hypertension were associated with low E:I ratio.
196	EDC (Pittsburgh, PA); 906 T1 youth with age of onset <18 years; onset 1965–1980; baseline 1986–1988; mean age at baseline 28 years; mean diabetes duration 19 years; follow-up through 2000	E:I ratio <1.1 and ≥2 symptoms	Cumulative incidence of symptomatic autonomic neuropathy by diabetes duration (years) and period of diabetes diagnosis Duration: Period of diagnosis — 20 / 25 1965–1969 — 22.0% / 49.0% 1970–1974 — 15.5% / 37.0% 1975–1980 — 10.5% / NA	70% participated; significant decline over diagnosis cohorts; relationship to declines in nephropathy are unclear.
256	SEARCH CVD study, two centers (CO, OH); 354 T1 youth with age of onset <20 years; mean diabetes duration 9.8 years; 176 nondiabetic, age-matched controls; 2009–2011	Heart rate variability (HRV) by SphygmoCor; markers of parasympathetic (PS) and sympathetic (S) loss	Heart rate variability Overall: T1 / Controls SDNN (ms) — 70.2 / 79.4 PS RMSSD (ms) — 63.7 / 77.7 HF power — 51.8 / 58.4 S overdrive LF power — 48.1 / 41.5	Clinic-based from population-based study; markers of reduced HRV, PS loss, and S overdrive all independent of traditional CVD risk factors; higher A1c, older age, female sex, higher triglycerides, and microalbuminuria predicted worse HRV among T1 youth.

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; E:I, expiratory:inspiratory ratio; EDC, Epidemiology of Diabetes Complications; HDL, high-density lipoprotein; HF, high frequency; HRV, heart rate variability; ICD, International Classification of Diseases; LDL, low-density lipoprotein; LF, low frequency; MNSI, Michigan Neuropathy Screening Instrument; NA, not applicable; NCV, nerve conduction velocities; PS, parasympathetic; RMSSD, root mean square successive difference of NN (or RR) intervals; S, sympathetic; SDNN, standard deviation of NN (or RR) intervals; SEARCH, SEARCH for Diabetes in Youth study; T1, type 1 diabetes; T2, type 2 diabetes; TPT, tactile perception threshold; VPT, vibration perception threshold.

SOURCE: References are listed within the table.

vibration testing on the foot, in 1,433 Australian youth with type 1 diabetes onset at age <18 years (211).

Most studies that have explored risk factors for DPN have found a major role for hyperglycemia. Importantly, reduction of A1c levels can reduce the incidence of DPN, as shown by the DCCT (245), where significant improvements occurred for all endpoints of both peripheral and autonomic neuropathy with intensive treatment. Cumulative incidence of confirmed clinical neuropathy at 5 years in the conventional group was 9.6% and was 2.8% in the intensive control group. At 13–14 years after DCCT closeout, clinical testing was repeated in 1,186 participants, and a lower risk of clinical distal symmetric neuropathy was noted, as well as improved nerve conduction values in the intensively treated cohort (246).

Type 2 Diabetes. There are remarkably few studies of DPN in youth with type 2 diabetes (Table 15.4). A SEARCH pilot study of 71 youth with type 2 diabetes found the prevalence of an abnormal Michigan Neuropathy Screening Instrument Exam to be 26% at a mean duration of 7.6 years, almost four times higher than among youth with type 1 diabetes (240). Similarly, in Australia, Eppens *et al*. reported on 68 type 2 diabetic youth with 1.3 years of duration (211). The prevalence of DPN using thermal and vibration testing was 21%, whereas it was 27% among comparable youth with type 1 diabetes. In a small clinical study of seven type 2 diabetic youth from the United Kingdom, 57% had abnormal clinical examinations after <2 years of duration (247). Constantino *et al*. reported on 354 youth in a large hospital cohort with onset at age 15–30 years in Sydney, Australia. They found that abnormal peripheral vibration perception thresholds were significantly higher in type 2 diabetic youth at an average 11.6 years of duration than type 1 diabetic youth ($p<0.0001$) at 14.7 years of duration (248). Dart *et al*. in Manitoba, Canada, compared type 2 and type 1 diabetic youth with onset at age 1–18 years starting in 1986 and followed through medical records for complications through 2007. Using only International Classification of Diseases (ICD) diagnostic codes for neuropathy, they found significantly shorter neuropathy-free survival ($p<0.001$) for type 2 versus type 1 diabetic youth, with 7.6% of type 2 diabetic youth having neuropathy compared with 5.0% of type 1 diabetic youth (208). These limited results point to the need for further population-based studies using standardized methods but suggest that DPN is more common among youth with type 2 diabetes than those with type 1 diabetes.

Cardiac Autonomic Neuropathy. Autonomic neuropathy in a person with diabetes can include cardiovascular, gastrointestinal, and urogenital signs and symptoms (249). In large clinic and population studies, the cardiovascular component (i.e., CAN) is usually studied. CAN is usually measured by simple "bedside" tests of heart rate variability (HRV) on standing, during a Valsalva maneuver, or deep breathing (the expiration:inspiration ratio) (250). In addition, spectral or other mathematic analysis of the electrocardiogram can provide evidence of various parameters that indicate altered nervous system function (251). In adults, such evidence of CAN was strongly related to excess cardiovascular mortality (252,253), though in youth, short-term mortality (over 2 years) was not related to CAN after accounting for nephropathy and hypertension (254).

Type 1 Diabetes. Limited studies of CAN in North American youth with type 1 diabetes exist (Table 15.4), though many data are available from relatively small European and Australian studies. In the Pittsburgh EDC cohort at baseline (255), the prevalence of reduced heart rate variability to expiration-inspiration was 37.5% among youth-onset type 1 diabetic youth with an average duration of 20 years (255). The long-term follow-up showed a cumulative incidence of 49% by 25 years of duration in the oldest cohort, but reduced incidence in more contemporary cohorts (196). The SEARCH CVD (cardiovascular disease) study reported that overall HRV was reduced in youth with type 1 diabetes at 10 years duration compared to controls, and there was evidence of both loss of parasympathetic tone and sympathetic overdrive (256). Like DPN, CAN was associated with poor glycemic control, higher triglyceride levels, and microalbuminuria (256). CAN was also associated with recurrent hypoglycemia (257). In youth with shorter duration (mean approximately 5 years), reduced HRV was correlated with long-term glycemia (over 4 years), but only in youth who were age ≥11 years (pubertal) (258). Nevertheless, CAN abnormalities were responsive to improvement in A1c levels as shown by the DCCT/EDIC at 13–14 years after DCCT closeout, where incident CAN was reduced by 31% through prior intensive treatment (259).

Type 2 Diabetes. No studies of autonomic neuropathy have been reported among youth with type 2 diabetes in the United States, and few worldwide (211,247). In a clinical study of seven type 2 diabetic youth, no autonomic abnormalities were found (247). Multiple studies in adults with type 2 diabetes have shown that CAN predicts mortality (255,260) and is prevalent, but often undetected clinically (249,261).

CARDIOVASCULAR RISK FACTORS

The cardiovascular risk factors discussed in this section include glycemic control, elevated blood pressure, dyslipidemia, and obesity. Since cardiovascular risk factors track from childhood to adulthood (262,263), and risk factors measured in youth predict adult target organ damage (264,265,266), it is important to evaluate them in youth prior to the onset of clinical complications. An adverse risk profile among youth with diabetes may magnify the already threefold excess risk for cardiovascular mortality associated with diabetes in adulthood (267). Following the discussion of risk factors, measures of subclinical CVD are reviewed, including arterial stiffness, carotid intima-media thickness (cIMT), and coronary artery calcification (CAC). Of interest, the vast majority of data suggest that the cardiovascular risk factor profiles and the

measures of subclinical CVD are usually worse in youth with type 2 diabetes than those with type 1 diabetes. Data from North American youth are summarized in Tables 15.5 and 15.6 and briefly discussed below.

Glycemic Control

Older observational studies of the role of glycemia and cardiovascular disease in youth-onset type 1 diabetes after 20–35 years of duration have been negative (196,268,269), though a report from Sweden showed a significantly reduced risk of CVD with lower A1c in adults with youth-onset type 1 diabetes and 1–35 years of duration (270). In addition, the DCCT/EDIC reported substantial reductions in coronary artery disease incidence with intensive control (271). Similarly, a meta-analysis of clinical trials in adults with type 1 and type 2 diabetes found a significant effect of improved glucose control on macrovascular outcomes (272). The RRR among adults with type 1 diabetes was 62% (95% CI 44%–74%) and was largely due to reduction of cardiac and peripheral vascular events (272). Among those with type 2 diabetes, the RRR was 19% due to reductions in stroke and peripheral vascular events (272). The effects appeared to be especially important among younger patients with shorter duration of diabetes, suggesting that improved glycemic control in youth and young adults may have long-lasting consequences, though almost no data have been reported on this topic (271). Whether improving glycemic control in more recent years has led to a reduction in CVD in cohorts with later onset remains unclear. The Pittsburgh EDC showed no change in the cumulative incidence of coronary artery disease at 20, 25, or 30 years of duration by year of diagnosis from 1950 to 1980 (196), although it did find significant reductions in nephropathy and mortality over the same period.

Observational studies among children and youth with diabetes generally report a constellation of related sociodemographic factors that are associated with poor glycemic control, including nonwhite race/ethnicity, lower socioeconomic status, lower parental educational attainment, less parental involvement in diabetes management, and impaired family dynamics (238,273,274,275,276,277). Limited data are available on glycemic control in large populations in North America. In SEARCH (203), poor glycemic control (A1c ≥9.5% [≥80 mmol/mol]) was seen with increasing age, as well as longer duration of diabetes and in minority youth. The same patterns were true for youth with type 1 or type 2 diabetes. Overall, 17% of type 1 diabetic youth had poor control, as did 27% of type 2 diabetic youth, who were older and had a higher proportion of minority youth (203). Moreover, worse glycemic control was seen in youth with type 1 diabetes on insulin regimens other than continuous subcutaneous insulin infusion (pumps) (175). For both type 1 and type 2 diabetes, higher A1c was also associated with higher concentrations of apolipoprotein B (Apo B) and smaller, more dense low-density lipoprotein (LDL) cholesterol particle size (278), as well as elevated ACR (220), suggesting possible links early in the history of diabetes between glycemic control and future risk for both macro- and microvascular disease.

Data on trends in glycemic control in North American youth with diabetes are even more limited. At the Joslin Clinic in Boston, Massachusetts, Svoren *et al.* established two cohorts of youth with type 1 diabetes enrolled from 1997–1998 and again in 2002–2003 and followed both for 2 years. Over this time, the later-onset cohort showed reduced A1c levels compared to the earlier cohort with increased use of self-glucose monitoring and multiple daily insulin injections (279). More extensive data from Europe show a similar trend. Youth with type 1 diabetes in Germany and Austria showed significant improvements in glycemic control over a 15-year period, 1995–2009 (181). The mean A1c decreased from 8.9% (74 mmol/mol) to 8.1% (65 mmol/mol), and the proportion of youth in poor control (A1c >9.0% [>75 mmol/mol]) decreased from 39.8% to 20.6%, due largely to an increase in youth receiving higher insulin doses through multiple daily injections or insulin pumps. Similar reductions in other European (181,280) and Australian centers (281) have been reported, though the Hvidoere Study Group, consisting of 21 clinics in 19 countries, showed no consistent changes in mean A1c over the period 1998–2005, with marked between-center differences not explained by a wide range of variables (282). Altogether, these data suggest that A1c remains unacceptably high among adolescents, and a significant proportion of these youth are not likely to see the benefits of reduced microvascular and macrovascular outcomes as they age into adulthood.

Elevated Blood Pressure

Hypertension in youth is typically diagnosed using age-, sex-, and height-specific blood pressure levels that are, on repeated measurement, ≥95th percentile of the blood pressure distribution (283). Most epidemiologic population studies, however, measure blood pressure at a single visit (284,285,286).

Type 1 Diabetes. Among 3,691 U.S. youth with type 1 diabetes, elevated blood pressure was present in 6.8% of those age <12 years and in 5.0% of those age ≥12 years (285), about that expected from the use of the 95th percentile for age. The frequency of hypertension was somewhat higher among minority youth (7.8% in African Americans, 7.6% in Hispanics, 13.1% in Asians and Pacific Islanders, and 11.8% in American Indians compared with 5.0% in non-Hispanic whites), in obese youth with BMI ≥95th percentile for U.S. youth (11.1%), and those with A1c ≥9.5% (8.4%) (285). Similarly, Australian youth with type 1 diabetes with a mean age of 15.7 years and diabetes duration of 6.8 years had a prevalence of hypertension of 16% (211). In the large German Diabetes Documentation System from 195 clinical centers and >27,000 youth with type 1 diabetes, the prevalence of hypertension was similar to nondiabetic youth at age 0–11 years but increased slightly in 12–16-year-olds (7.4%) and was 11.0% in 17–27-year-olds (287).

TABLE 15.5. Cardiovascular Risk Factors in Youth With Diabetes

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
GLYCEMIC CONTROL				
Type 1 diabetes				
279	Joslin Diabetes Center, Boston, MA; two cohorts enrolled in 1997–1998 (N=299) and 2002–2003 (N=152); T1 youth age 8–16 years at exam; mean diabetes duration 5–6 years; 2 years follow-up		Mean A1c levels by period of diabetes diagnosis 1997–1998 / 2002–2003 Baseline 8.7% / 8.4% Follow-up 9.0% / 8.7%	Clinic-based sequential recruitment; A1c control improved in later cohort with greater use of self-glucose monitoring and multiple insulin injections.
203	SEARCH, six U.S. centers; 3,947 T1 youth with age of onset <20 years; 2001–2005	Good control: age-specific ADA criteria, usually <7.5%, except age <12 years when higher Poor control: A1c ≥9.5%	Prevalence of poor control Age (years) at exam 0–5 8.0% 6–12 11.3% 13–18 23.3% 19–22 28.5% Diabetes duration (months) <12 7.5% 12–23 15.1% 24–47 18.1% ≥48 25.3% Race/ethnicity White 12.3% Black 35.5% Hispanic 27.3% Asian and Pacific Islander 26.0% American Indian 52.2%	Population-based registry; 47% response to exam.
Type 2 diabetes				
203	SEARCH, six U.S. centers; 552 T2 youth with age of onset <20 years; 2001–2005	Good control: age-specific ADA criteria, usually <7.5%, except age <12 years when higher Poor control: A1c ≥9.5%	Prevalence of poor control Age (years) at exam 6–12 15.6% 13–18 23.0% 19–22 47.2% Diabetes duration (months) <12 12.6% 12–23 23.2% 24–47 36.3% ≥48 48.9% Race/ethnicity White 12.2% Black 22.3% Hispanic 27.4% Asian and Pacific Islander 36.4% American Indian 43.8%	Population-based registry; 47% response to exam.
ELEVATED BLOOD PRESSURE				
Type 1 diabetes				
285	SEARCH, six U.S. centers; 3,691 T1 youth with age of onset 3–20 years; 2002–2005	SBP or DBP ≥95th percentile for age, sex, and height, regardless of medication. Normal weight: <85th percentile; overweight: 85th–94.9th percentile; obese: ≥95th percentile of U.S. youth	Prevalence of hypertension Age (years) <12 6.8% ≥12 5.0% Male 5.7% Female 6.1% Race/ethnicity White 5.0% Black 7.8% Hispanic 7.6% Asian and Pacific Islander 13.1% American Indian 11.8% Normal weight 4.8% Overweight 6.3% Obese 11.1% A1c <7.5% 4.3% 7.5%–9.5% 5.2% ≥9.5% 8.4%	Population-based; 47% of eligible had examination; only 7% of those with hypertension were aware of their condition, and only 1.5% were treated.

Table 15.5 continues on the next page.

TABLE 15.5. (continued)

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
Type 2 diabetes				
285	SEARCH, six U.S. centers; 410 T2 youth with age of onset 3–20 years; 2002–2005	SBP or DBP ≥95th percentile for age, sex, and height, regardless of medication. Normal weight: <85th percentile; overweight: 85th–94.9th percentile; obese: >95th percentile of U.S. youth	Prevalence of hypertension Age (years) <12 ... 27% ≥12 ... 23% Male ... 25% Female ... 23% Race/ethnicity White ... 20% Black ... 28% Hispanic ... 22% Asian and Pacific Islander ... 27% American Indian ... 21% Normal weight ... 0% Overweight ... 17% Obese ... 27% A1c <7.5% ... 20% 7.5%–9.5% ... 29% ≥9.5% ... 24%	Population-based; 47% of eligible had examination; only 32% of those with hypertension were aware of their condition, and 11.8% were treated.
286	Winnipeg, Manitoba, Canada, specialty clinic; 99 T2 youth age 7–17 years at exam; 95% First Nation; mean diabetes duration 2.2 years; 1997–2002	Chart review of clinical parameters; abnormal is >95th percentile of NHANES reference population.	Prevalence of hypertension SBP ... 13% DBP ... 6%	Clinic-based, but clinic cares for a high proportion of all cases of diabetes in the geographic region.
DYSLIPIDEMIA				
Type 1 diabetes				
292	Colorado, specialty clinic; 682 T1 youth age <21 years; 2000–2004	Abnormal: TC ≥200 mg/dL HDL ≤35 mg/dL	Prevalence of abnormal lipids Diabetes / NHANES TC ... 15.4% / 11.2% HDL ... 3.5% / 5.7% Either abnormal ... 18.6% / 16.3%	Clinic-based; T1 had physician diagnosis or antibodies; lipids drawn after 1 month of diabetes onset; higher A1c predicted TC (p<0.001) and lower HDL (p=0.052).
361	CACTI study, CO; 652 T1 persons age 19–56 years; mean diabetes duration 23.2 years; 764 nondiabetic controls; 2000–2002	TC ≥200 mg/dL LDL ≥130 mg/dL TG ≥150 mg/dL HDL ≤40 mg/dL or medication	Percent with dyslipidemia Cases ... 47% Controls ... 58%	Clinic-based with controls; of persons on treatment, only 41% of T1 persons and 15% of controls with dyslipidemia were controlled by diet or medication.
293	SEARCH, six U.S. centers; 2,165 T1 youth with age of onset 3–20 years, age 10–22 years at exam; 2001–2002	Lipids measured at central laboratory for all sites	Percent abnormal lipid levels by age (years) at exam TC / <10 / 10–19 <170 ... 54% / 50% 170–199 ... 34% / 31% ≥200 ... 12% / 19% HDL <40 ... 7% / 12% 41–59 ... 51% / 57% ≥60 ... 43% / 31% TG ≤100 ... 95% / 76% 100–199 ... 5% / 20% 200–399 ... 0% / 4% ≥400 ... 0% / 1%	Population-based; only 43% of entire population eligible had a visit; 19% had TC greater than recommended.
294	SEARCH, six U.S. centers; 1,680 T1 youth with age of onset 3–19 years; age 10–22 years at exam; 2001–2004	Percent greater than cut point shown: TC ≥200 mg/dL LDL ≥130 mg/dL HDL <40 mg/dL TG ≥150 mg/dL Non-HDL ≥160 mg/dL	Percent abnormal lipid levels by A1c <6.7% / ≥9.5% TC ... 11% / 35% LDL ... 10% / 27% HDL ... 14% / 14% TG ... 1% / 20% Non-HDL ... 4% / 22%	Population-based; 43% with study visit; strong association with higher A1c and worse lipids, except for HDL.

Table 15.5 continues on the next page.

TABLE 15.5. (continued)

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
278	SEARCH, six U.S. centers; 2,657 T1 youth with age of onset 3–19 years; 2001–2004	Elevated Apo B: ≥100 mg/dL Dense LDL: Rf ≤0.237 LDL: ≥130 mg/dL	Percent abnormal All / A1c ≥9.5% Apo B 11% / 28% Rf 8% / 18% LDL 12% / NA	Population-based; dense LDL and Apo B increased with higher A1c.
295	SEARCH Case-Control study (CO, SC); 164 T1 youth age 10–22 years, mean age 13.9 years, diabetes duration 2.2 years; 188 nondiabetic controls, mean age 14.4 years; 2003–2006	Poor control: A1c ≥7.5% Good control: A1c <7.5% Abnormal: TC ≥200 mg/dL LDL ≥130 mg/dL TG ≥150 mg/dL HDL ≤35 mg/dL Apo B ≥90 mg/dL LDL Rf ≤0.237	Percent with abnormal lipid levels by glycemic control Poor / Good / Controls TC 15.6% / 7.4% / 8.6% LDL 12.1% / 7.3% / 8.2% TG 8.7% / 1.3% / 8.4% HDL 5.0% / 7.6% / 10.3% Apo B 20.4% / 10.3% / 4.6% LDL 22.7% / 24.9% / 10.6%	64% of eligible participated; cases in good control had similar lipids to controls, except for higher Apo B and small dense LDL (Rf ≤0.237).
296	SEARCH, six U.S. centers; 1,193 T1 youth with age of onset 3–19 years; prospective follow-up of ~2 years; at least two exams; 2002–2005	Association of change in glycemic control to change in level of lipids over time; example is at A1c 8.0% at 6 months follow-up	Change in A1c / Change in TC (mg/dL) +1% / +6.9 +2% / +12.3 -1% / -3.9 -2% / -9.3	Population-based; all lipids (TC, LDL, HDL, non-HDL) significantly associated with changes in A1c over time; higher A1c at baseline had larger effects on change; increasing A1c over time had greater effect on change in lipids.
Type 2 diabetes				
294	SEARCH, six U.S. centers; 283 T2 youth with age of onset <20 years, age 10–22 years at exam; 2001–2002	Lipids measured at central laboratory for all sites	Percent with abnormal lipid levels TC <170 39% 170–199 29% ≥200 33% HDL <40 44% 41–59 49% ≥60 7% TG ≤100 37% 100–199 37% 200–399 17% ≥400 9%	Population-based; only 43% of entire population eligible had a visit; 19% had TC greater than recommended.
286	Winnipeg, Manitoba, Canada, specialty clinic; 99 T2 youth age 7–17 years; 95% First Nation; mean diabetes duration 2.2 years; 249 First Nation youth controls without diabetes; 1997–2002	Chart review of clinical lipid parameters; abnormal is >75th or <25th percentile of NHANES reference population.	Percent with abnormal lipid levels Cases / Controls TC 76% / 60% TG 66% / 43% LDL 74% / 41% Apo B 72% / 43% HDL 52% / 35%	Clinic-based, but clinic cares for a high proportion of all cases of diabetes in the geographic region.
294	SEARCH, six U.S. centers; 283 T2 youth with age of onset 3–20 years; age 10–22 years at exam; 2001–2004	Percent greater than cut point shown: TC ≥200 mg/dL LDL ≥130 mg/dL HDL <40 mg/dL TG ≥150 mg/dL Non-HDL ≥160 mg/dL	Percent with abnormal lipid levels by A1c <6.7% / ≥9.5% TC 14% / 65% LDL 14% / 43% HDL 43% / 44% TG 21% / 60% Non-HDL 37% / 62%	Population-based; 43% with study visit; strong association with higher A1c and worse lipids, except for HDL.
278	SEARCH, six U.S. centers; 345 T2 youth with age of onset 3–19 years; 2001–2004	Elevated Apo B: ≥100 mg/dL Dense LDL: Rf ≤0.237 LDL: ≥130 mg/dL	Percent with abnormal lipid levels All / A1c ≥9.5% Apo B 36% / 72% Rf 36% / 62% LDL 23% / NA	Population-based; dense LDL and Apo B increased with higher A1c.

Table 15.5 continues on the next page.

TABLE 15.5. (continued)

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
OBESITY AND INSULIN RESISTANCE				
Type 1 diabetes				
298	Children's Hospital of Pittsburgh, PA; 185 T1 youth with age of onset <19 years; black (N=96) and white (N=89); 1979–1998	Overweight ≥85th percentile (CDC) by chart review	Prevalence of overweight by year of diabetes onset 1979–1989 / 1990–1998 All 12.6% / 36.8% Age (years) <11 7.3% / 22.2% ≥11 20.0% / 50.0% White 2.9% / 16.6% Black 22.0% / 55.0% Ab+ 5.1% / 24.4% Ab- 46.1% / 75.0%	Hospital-based; high proportion of new-onset cases are hospitalized at this hospital.
20	SEARCH, six U.S. centers; 3,524 T1 youth with age of onset <20 years; 2001–2004	Obese: BMI ≥95th percentile Overweight: BMI 85th–<95th percentile (CDC)	Prevalence Obese — Cases / NHANES All 12.6% / 16.9% White 10.7% / 15.8% Black 20.1% / 20.2% Hispanic 17.0% / 18.3% Overweight All 22.1% / 16.1% White 20.8% / 15.9% Black 23.4% / 14.8% Hispanic 28.0% / 18.8%	Population-based; 47% of eligible youth had examination.
362	Barbara Davis Center, Denver, CO; 292 T1 youth, mean age 15.4 years; mean diabetes duration 8.8 years; 89 nondiabetic controls; 2008–2010	Insulin sensitivity score (IS) using age, waist, A1c, and TG	Tertiles of IS score showed that T1 youth had similar cardiovascular risk factor distribution in most insulin sensitive tertile; linear increase in atherogenicity as IS decreased among T1 youth.	Clinic-based; ~80% of all cases in state cared for; T1 youth had lower IS score than controls (7.8 vs. 11.5, p<0.0001).
Type 2 diabetes				
20	SEARCH, six U.S. centers; 429 T2 youth with age of onset <20 years; 2001–2004	Obese: BMI ≥95th percentile Overweight: BMI 85th–<95th percentile (CDC)	Prevalence Obese — Cases / NHANES All 79.4% / 16.9% White 68.8% / 15.8% Black 91.1% / 20.2% Hispanic 75.0% / 18.3% Overweight All 10.4% / 16.1% White 13.9% / 15.9% Black 8.0% / 14.8% Hispanic 10.5% / 18.8%	Population-based; 47% of eligible youth had examination.
286	Winnipeg, Manitoba, Canada, specialty clinic; 99 T2 youth age 7–17 years; 95% First Nation; mean diabetes duration 2.2 years; 1997–2002	Chart review of clinical parameters Overweight: BMI 85th–<95th percentile (CDC) Obese: BMI ≥95th percentile	Prevalence Overweight 44% Obese 39% Overweight + obese 83%	Clinic-based, but clinic cares for a high proportion of all cases of diabetes in the geographic region.

Conversions for A1c, cholesterol, and triglyceride values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; Ab, antibody; ADA, American Diabetes Association; Apo B, apolipoprotein B; BMI, body mass index; CACTI, Coronary Artery Calcification in Type 1 Diabetes study; CDC, Centers for Disease Control and Prevention; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IS, insulin sensitivity; LDL, low-density lipoprotein; NA, not available; NHANES, National Health and Nutrition Examination Survey; Rf, relative flotation (gradient centrifugation); SBP, systolic blood pressure; SEARCH, SEARCH for Diabetes in Youth study; T1, type 1 diabetes; T2, type 2 diabetes; TC, total cholesterol; TG, triglycerides.

SOURCE: References are listed within the table.

Type 2 Diabetes. In contrast, among 410 youth with type 2 diabetes in SEARCH, 23.7% had elevated blood pressure, with higher prevalence in minority and overweight/obese youth compared with only 5%–7% of type 1 diabetic youth of the same age and somewhat longer diabetes duration (285). Among youth with hypertension, only 32% were aware of their condition, and only 12% had been treated (285), similar to that seen in Germany (287). Sellers *et al*. reported on 99 youth with type 2 diabetes from Winnipeg, 95% of whom were First Nation (aboriginal) youth (286). Elevated systolic blood pressure was seen in 13% of cases, but only 6% had elevated diastolic blood pressure. Similar to the SEARCH findings, Australian youth with type 2 diabetes and only 1.3 years of diabetes duration had a hypertension prevalence of 36% compared to 16% in type 1 diabetes in the same clinic (211). In another Australian center, the prevalence of antihypertensive treatment after 11.6 years of duration for youth with type 2 diabetes was 49.3% but was only 24.6% among youth with type 1 diabetes and 14.7 years of duration (248). Given the high levels of obesity in most youth with type 2 diabetes, some of the detected hypertension may have preceded the development of diabetes.

Among adults with type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) has shown reductions in risk of 24% in diabetes-related endpoints, 32% in deaths related to diabetes, 44% in strokes, and 37% in microvascular endpoints in the group assigned to tight blood pressure control compared with that assigned to less tight control (288). There are no long-term trials of hypertension control in youth with diabetes followed into adulthood, which need to be conducted. Given evidence of early target organ damage in children and adolescents with diabetes (see the section *Subclinical Cardiovascular Disease*), it is prudent to carefully monitor and initiate treatment of hypertension in youth (283) to likely reduce cardiovascular endpoints later in life.

Dyslipidemia

Various lipid fractions are increasingly measured in youth (289), given that lipids track from youth into adulthood (262) and because of the known onset of fatty streaks and early plaques in arteries of even young children (290). These lipid fractions include total cholesterol, HDL cholesterol, LDL cholesterol, very-low-density lipoprotein (VLDL) cholesterol, triglycerides, Apo B (a marker of higher cardiovascular risk in adults), as well as the density of LDL cholesterol (with small dense LDL cholesterol conferring higher risk) and oxidized lipoprotein fractions.

Specific dyslipidemias do not appear to exist in type 1 diabetes, especially in youth, where most studies have found few differences compared with controls (291). However, among youth with type 2 diabetes, patterns typically seen in adults with type 2 diabetes (low HDL cholesterol, high triglycerides, small dense LDL cholesterol) are also common (291).

Type 1 Diabetes. In a large clinic cohort in Colorado, few differences in lipid levels were observed in youth with type 1 diabetes compared with NHANES youth (292). However higher A1c was associated with higher total cholesterol and lower HDL cholesterol. In 2,165 youth with type 1 diabetes, 19% of those age 10–19 years had total cholesterol ≥200 mg/dL (≥5.18 mmol/L), 12% had HDL cholesterol <40 mg/dL (<1.04 mmol/L), and 5% had triglycerides ≥200 mg/dL (≥2.26 mmol/L) (293). Lipids were significantly higher in youth with poor glycemic control, except HDL cholesterol, which was not associated with A1c (294). Similarly, Albers *et al*. reported that SEARCH youth with both type 1 and type 2 diabetes and poor control had elevated levels of both ApoB and small dense LDL cholesterol, the most atherogenic fractions (278). The effect of poor control was also shown in a subset of SEARCH participants in Colorado and South Carolina (the SEARCH Case-Control Study), where youth with type 1 diabetes in good control had traditional lipid patterns similar to controls, while those with poor glycemic control had elevated levels. However, ApoB and small dense LDL cholesterol were higher in youth with type 1 diabetes than in controls, even among youth in good glycemic control (295). Thus, even if absolute levels of total and LDL cholesterol appear similar in youth with type 1 diabetes and controls, those in poor glycemic control have more atherogenic lipid profiles. Maahs *et al*. have extended these cross-sectional observations and shown that changes in A1c levels over a 2-year period were significantly associated with parallel changes in lipids (296). For example, an improvement in A1c of 1% over 2 years (from 8.0% to 7.0%) lowered total cholesterol by 3.9 mg/dL (0.10 mmol/L) (296). Therefore, glycemic control and lipids are prospectively related, and better control reduces lipid levels.

Type 2 Diabetes. Lipid abnormalities in youth with type 2 diabetes were higher than controls in several studies. Among 283 youth with type 2 diabetes in SEARCH, 33% had total cholesterol ≥200 mg/dL, 44% had low HDL cholesterol, and 26% had triglycerides ≥200 mg/dL, much higher than among type 1 diabetic youth in the same study (293). Very strong cross-sectional associations between A1c level and lipid levels were also reported (294). An elevated total cholesterol (≥200 mg/dL) among youth in good control (A1c <6.7% [<50 mmol/mol]) was seen in 14% of type 2 diabetic youth compared to 65% in those with A1c ≥9.5% (294). This was also true for small dense LDL cholesterol and Apo B (278). A similar pattern among First Nation youth in Manitoba was seen, with significant differences from controls for all measured lipids (286). Youth with type 2 diabetes have substantially worse lipid profiles than nondiabetic youth of the same age.

Obesity and Insulin Resistance

Obesity and accompanying insulin resistance play a significant role in the development of cardiovascular endpoints and likely contribute to the excess of CVD risk and mortality excess in persons with diabetes. As the worldwide population of

children has become more overweight and obese, so too have youth with both type 1 and type 2 diabetes.

Type 1 Diabetes. Two U.S. studies have documented the increasing prevalence of obesity in youth with diabetes. Comparing the prevalence of overweight and obesity in youth with type 1 diabetes to NHANES data, SEARCH showed that the prevalence of obesity was similar among youth with and without diabetes, while the prevalence of overweight was substantially higher in all race/ethnicity groups with diabetes (20). This excess adiposity also increased insulin resistance in youth with type 1 diabetes (297). In Pittsburgh, data on overweight among youth with type 1 diabetes onset in 1979–1989 were compared to data from 1990–1998 cohorts (298). A tripling of overweight was noted in both antibody-positive (type 1 diabetes) and antibody-negative (possible type 2 diabetes) youth. Prevalence of overweight was greatest in African Americans in both time periods.

Type 2 Diabetes. One of the hallmarks of the presentation of type 2 diabetes in youth is obesity (90). In SEARCH, 70%–90% of youth with type 2 diabetes were obese compared to 15%–20% of the U.S. population (20). Similarly, in Canadian First Nation youth with type 2 diabetes, overweight and obese youth made up 83% of the population (286). In Australian youth with type 2 diabetes, 81% were overweight or obese compared to only 32% of youth with type 1 diabetes (211). Hyperinsulinemic euglycemic clamps have been conducted in youth with type 2 diabetes and obese controls to assess insulin sensitivity and beta cell function directly (299). Youth with type 2 diabetes had defects in both first and second phase insulin secretion and were substantially less insulin sensitive than obese controls, much the same as in adults.

SUBCLINICAL CARDIOVASCULAR DISEASE

Noninvasive techniques are used to evaluate arterial structure and function well before diabetes-related vascular disease becomes irreversible (300,301,302,303,304,305). A variety of subclinical markers of early CVD have been explored in youth with diabetes, including measures of arterial stiffness, arterial thickness (e.g., cIMT), and CAC. Studies in North American youth are summarized in Table 15.6.

Arterial Stiffness

Arteriosclerosis increases pulse-wave velocity (PWV) and can augment central arterial pressure due to early pressure wave reflection (302). Higher PWV and estimates of augmented arterial pressure, as well as brachial distensibility, have been used to explore arterial stiffness. An additional indirect measure of stiffness is pulse pressure (the difference between systolic and diastolic blood pressure), which is elevated in adults with youth-onset type 1 diabetes and predicts cardiovascular endpoints (306). PWV is associated with cardiovascular risk factors (307) and predicts mortality in both type 1 and type 2 diabetic adults independent of traditional cardiovascular risk factors and glycemic control (308). Thus, the finding of these abnormalities in youth with diabetes to a greater extent than among nondiabetic youth provides clues to the earlier onset and progression of CVD.

Type 1 Diabetes. Three studies in youth with type 1 diabetes found measures of arterial stiffness to be greater in them than in nondiabetic controls (309,310,311,312). In addition, youth with type 1 diabetes with lower HRV (a marker of CAN) had increased peripheral and central measures of stiffness (312). Several European studies also found various measures of increased stiffness in type 1 diabetic youth in some (313,314,315,316,317,318), though not all (319,320,321), studies.

Type 2 Diabetes. Studies of arterial stiffness in youth with type 2 diabetes usually include fewer participants than those in type 1 diabetic youth, but several have found PWV to be higher (greater stiffness) than among controls (322) or compared to type 1 diabetic youth of similar age and diabetes duration (311). Peripheral measures of stiffness (brachial artery distensibility [BrachD], augmentation index [AIx]) were also worse among type 2 than type 1 diabetic youth (311). Shah *et al*. studied 215 non-Hispanic white and African American youth with type 2 diabetes in Cincinnati, Ohio, and found African Americans to have greater arterial stiffness than non-Hispanic whites (323). Interestingly, A1c was not associated with stiffness in either group, but age, obesity, and blood pressure were associated in both race/ethnicity groups, and lower HDL cholesterol and higher triglycerides were associated in non-Hispanic whites, suggesting that traditional cardiovascular risk factors play an important role in arterial stiffness in youth with type 2 diabetes. Consistent with this concept was the finding that the small artery elasticity index was 24% higher among youth with type 2 diabetes than in lean controls but was not different from obese controls (324). Functional measures of the arterial tree (stiffness markers) are clearly affected in youth with both types of diabetes, and cardiovascular risk factors play an important role.

Carotid Intima Medial Thickness

A commonly used structural measure of the arterial tree is the carotid vessel wall intima-medial thickness (cIMT), usually measured by B-mode ultrasound in the carotid arteries (325). As seen in Table 15.6, absolute measures of cIMT vary substantially between studies (e.g., 0.32–0.57 mm), when differences between cases and controls are often measured in hundredths of a millimeter.

Type 1 Diabetes. No difference in cIMT was seen in a small study of youth with type 1 diabetes from Michigan, but less flow-mediated dilatation was seen in cases (326). A larger study from California found significantly thicker cIMT in type 1 diabetic cases than controls but found few expected risk factor correlates (327). In the largest study to date, the SEARCH

TABLE 15.6. Subclinical Cardiovascular Disease in Youth With Diabetes

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
ARTERIAL STIFFNESS				
Type 1 diabetes				
309	Gainesville, FL; 98 T1 youth age 10–18 years; 57 age-matched nondiabetic controls	Radial artery tonometry using SphygmoCor for augmentation index (AIx) and corrected to heart rate of 75 beats/min	Radial artery tonometry Cases / Controls AIx: 1.11 / -0.47 AIx75: 1.88 / -3.31	Clinic/camp-based; higher AIx means stiffer vessels.
310, 311	SEARCH, two centers (OH, CO); 535 T1 youth with age of onset <20 years; mean age 14.6 years; mean diabetes duration 5.4 years; 241 nondiabetic controls age ≥10 years from Ohio	AIx over R radial artery corrected to heart rate of 75 beats/min with SphygmoCor; BrachD (% Δ/mmHg) with DynaPulse for arterial distensibility.	PWV carotid-femoral (m/s) Cases / Controls BrachD: 6.11 / 7.0 AIx75: 2.07 / -0.52 PWV-trunk*: 5.42 / 5.11 ≥1 measure abnormal†: 32.3% * Age-adjusted † Used ≤10th, ≥90th percentiles of normals as abnormal	Population-based original cohort; no estimate of response rate; lower BrachD, higher AIx, and higher PWV indicate stiffer vessels in cases than controls.
312	SEARCH CVD (OH, CO); 344 T1 youth with age of onset <20 years; mean age 14.6 years; mean diabetes duration 5.4 years; 171 nondiabetic controls	PWV carotid-femoral in m/s; AIx heart rate variability (HRV) with SphygmoCor; BrachD (% Δ/mmHg) with DynaPulse	Lower HRV measures were associated with peripheral and central stiffness; measures were attenuated with adjustment for CVD risk factors but significant for BrachD and PWV. Lower HRV was not associated with increased central stiffness or AIx75 in controls.	Population-based original cohort; lower BrachD, higher AIx, and higher PWV indicate stiffer vessels; lower HRV indicative of autonomic neuropathy.
Type 2 diabetes				
322	Children's Hospital Pittsburgh, PA; 20 T2 youth, mean age 15.5 years; mean diabetes duration 1.7 years; antibody-negative; 22 normal weight, 20 obese controls	Aortic PWV (location not specified) in cm/s	Aortic PWV (cm/s) T2: 769 Obese: 584 Normal: 497	Convenience sample; aPWV associated with higher HOMA-IS and A1c; no differences in cIMT between groups – small sample size
332	Cincinnati Children's Hospital, OH; 128 T2 antibody-negative youth age 10–24 years; 182 lean (BMI <85th percentile) and 136 obese controls (BMI >95th percentile for U.S. youth and young adults)	Carotid stiffness by M mode: Young elastic modulus (YEM, mmHg/mm) and beta stiffness index (unitless)	Carotid stiffness T2 / Obese / Lean YEM: 100.8 / 105.2 / 83.8 Beta: 1.08 / 1.12 / 0.96	Clinic-based; both T2 and obese youth had stiffer carotids than lean youth.
311	SEARCH two sites (OH, CO); 60 T2 youth with age of onset <20 years; mean age 14.6 years; mean diabetes duration 5.4 years	AIx corrected to heart rate of 75 beats/min with SphygmoCor; higher levels are stiffer; BrachD (% Δ/mmHg) with DynaPulse	PWV carotid-femoral (m/s) BrachD: 5.2 AIx75: 6.4 PWV-trunk: 6.4	Population-based original cohort; no estimate of response rate; lower BrachD, higher AIx, and higher PWV indicate stiffer vessels; more stiffness mediated by increased adiposity and blood pressure compared to T1 youth and overall.
323	Cincinnati Children's Hospital clinic, OH, and regionally; 215 T2 youth age ≥11 years; mean age 18 years; mean diabetes duration 3.5 years; most antibody-negative	AIx with SphygmoCor; higher levels are stiffer; PWV [carotid-femoral (m/s)] with SphygmoCor	Stiffness measures Whites / Blacks PWV: 6.21 / 6.96 AIx (%): 4.44 / 7.64	Clinic-based; among white youth: age, obesity, blood pressure, HDL, and TG independently predicted stiffness; among black youth: age, blood pressure, and obesity were predictive; A1c was not predictive in either race.
324	Oklahoma City, OK; 34 T2 youth age 10–18 years; 58 obese (>95th percentile) and 50 normal weight (25th–75th percentile of U.S. youth) controls	Elasticity index of small and large arteries (SAEI, LAEI) by pulse-wave analysis; reactive arterial tonometry (RH-PAT)	SAEI 24% higher for T2 youth than normal controls; not different from obese controls; LAEI not different in T2 youth, normal, and obese controls; no differences in the reactive hyperemia index.	Clinic-based; linear increase in SAEI and LAEI to age 16.5 years, then decline to age 18 years, suggesting early maturation of vascular system; among T2 youth, fasting glucose was associated with worse endothelial function; 80% of T2 youth were on metformin, which improves endothelial dysfunction and may have resulted in little difference from controls.

Table 15.6 continues on the next page.

TABLE 15.6. (continued)

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
CAROTID INTIMA-MEDIA THICKNESS				
Type 1 diabetes				
326	Children's Hospital of Michigan, Detroit, MI; 31 T1 youth; mean age 15 years; mean diabetes duration 6.8 years; 35 age-matched nondiabetic controls	Far wall, common carotid; five images averaged from left and right side, in mm; brachial artery vascular reactivity as flow mediated artery dilation (FMD)	Cases / Controls cIMT: 0.33 / 0.32 Change in FMD: 0.13 / 0.25* * p<0.0001	Clinic-based; no difference in cIMT between groups, sample size small; less FMD in T1 youth than controls; no difference in endothelium-independent (nitroglycerin challenge).
327	Children's Hospital, Orange County, CA; 142 T1 youth; mean age 16 years; mean diabetes duration 7.3 years	Right distal common carotid far wall IMT, in mm	All / Male / Female Cases: 0.564 / 0.572 / 0.558 Controls: 0.540 / 0.545 / 0.537	Hospital-based; no correlation with age, Tanner stage, duration, BMI, blood pressure, A1c, or lipids; A1c had positive correlation with TC, Apo B, and HDL.
328	SEARCH CVD study (OH, CO); 402 T1 youth; mean age 18.9 years; 206 matched controls	B-mode cIMT measured in common, bulb, and internal carotid, in mm; M mode common carotid stiffness (Beta)	Cases / Controls Bulb (mm): 0.461 / 0.445 Beta stiffness: 2.15 / 2.27	Sample drawn from population-based study; bulb IMT significantly different from controls when adjusted for cardiovascular risk factors, not in stiffness index; adjustment for A1c removed IMT differences between cases and controls.
Type 2 diabetes				
332	Cincinnati Children's Hospital, OH; 128 T2 antibody-negative youth age 10–24 years; 182 lean (BMI <85th percentile) and 136 obese controls (BMI >95th percentile for U.S. youth and young adults)	Three B-mode images on left, right sides averaged for common, bulb, and internal carotid, in mm	Location / T2 / Obese / Lean Common: 0.54 / 0.50 / 0.52 Bulb: 0.52 / 0.48 / 0.47 Internal: 0.44 / 0.42 / 0.39	Clinic-based; T2 youth had significantly greater cIMT for all segments than lean youth and thicker common and bulb cIMT than obese youth; both T2 and obese youth were thicker than lean for internal cIMT.
334	Cincinnati Children's Hospital, OH; 129 T2 youth age 10–23 years; mean diabetes duration 4.4 years; 96% antibody-negative; non-insulin requiring; no controls; 2007–2008	Average of left, right sides for common carotid, bulb, and internal carotid, in mm	Location / Male / Female Common: 0.58 / 0.52 Bulb: 0.55 / 0.51 Internal: 0.48 / 0.48	Clinic-based; males had thicker cIMT than females; older age, higher A1c, and male sex were associated with thicker common cIMT; diabetes duration significant for bulb and internal cIMT; also higher DBP and LDL associated with internal cIMT.
CORONARY ARTERY CALCIFICATION (CAC)				
Type 1 diabetes				
363	EDC, Pittsburgh PA; 302 youth-onset T1; mean age 38.1 years; onset 1950–1980; 10-year follow-up visit; 1997–1998	EBCT; positive: CAC score >400	CAC prevalence (%)* Age (years) / Male / Female 18–29: 11 / 15 30–39: 29 / 30 40–49: 75 / 60 50–55: 88 / 65 * Among those without clinical CAD	Hospital-based but representative of Allegheny County registry; CAC higher in all age groups when CAD present.
337	Morristown, NJ; 101 T1 youth age 17–29 years; ≥5 years diabetes duration; 2002	Forty 3 mm slices by EBCT; positive: CAC scores >0	Prevalence of positive CAC All: 10.9% Men: 15.1% Women: 6.3%	Clinic-based; mean score among positives was 12.5 (range 1–95.8); smokers had fivefold higher prevalence of CAC; CAC was not associated with A1c, duration, BMI, or microalbuminuria.
339	CACTI, Denver, CO; 656 T1 persons age 20–55 years; mean diabetes duration 23 years; 764 nondiabetic controls; 2000–2002	EBCT for CAC; abnormal score >0; insulin resistance by equation, including waist/hip ratio, A1c, and hypertension	OR for CAC, T1 to controls; prevalence of CAC; age 20–29 years Men / Women OR: 2.1 / 3.6 Prevalence: 24% / 14%	Clinic-based; insulin resistance, lipids, and A1c explained most of the excess CAC in T1 women.

Table 15.6 continues on the next page.

TABLE 15.6. (continued)

REFERENCE	POPULATION; YEARS	METHOD	OUTCOME	COMMENTS
340	CACTI, Denver, CO; 109 T1 persons age 20–55 years; mean diabetes duration 23 years; follow-up for 2.7 years; 1997–2000	Repeat EBCT for CAC; abnormal score >0; progression: ≥2.5 square root transformed calcium volume, which accounts for variability	OR for CAC progression associated with baseline A1c ≥7.5% ..... 7.1 CAC ..... 9.7 T1 duration ..... 3.2 Male sex ..... 3.9 Age 1.7	Clinic-based; multivariate model; strong association of poor glycemic control; also, persons with higher BMI and more insulin dose had higher CAC risk in the same model.
338	EDC, Pittsburgh, PA; 222 youth-onset T1; mean age 38.1 years; onset 1950–1980; 4-year follow-up from first CAC; 1997–2005	CAC progression was >2.5 increase in square root transformed Agatston score	110 of 222 progressed (49.5%)	Hospital-based but representative of Allegheny County registry; CAC progression was not related to A1c level; diabetes duration, baseline CAC level, BMI, non-HDL cholesterol, and albumin excretion rate were all significant independent predictors of progression.

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; AIx, augmentation index (stiffness); Apo B, apolipoprotein B; BMI, body mass index; BrachD, brachial artery distensibility; CAC, coronary artery calcification; CACTI, Coronary Calcification in Type 1 Diabetes study; CAD, coronary artery disease; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; DBP, diastolic blood pressure; EBCT, electron beam computed tomography; EDC, Epidemiology of Diabetes Complications study; FMD, flow-mediated artery dilation; HDL, high-density lipoprotein; LDL, low-density lipoprotein cholesterol; OR, odds ratio; PWV, pulse wave velocity (stiffness); SBP, systolic blood pressure; SEARCH, SEARCH for Diabetes in Youth study; T1, type 1 diabetes; T2, type 2 diabetes; TG, triglyceride.

SOURCE: References are listed within the table.

CVD study measured 402 type 1 diabetic youth and 206 matched controls from Colorado and Ohio and found that carotid bulb IMT was significantly thicker than that in controls, with no differences at other locations (common, internal). This difference remained after adjustment for cardiovascular risk factors but was removed after adjustment for A1c (328). A review of 15 cIMT and type 1 diabetes studies (including one shown in Table 15.6 (326)) found that in eight of them, significant thickening of cIMT was seen in cases compared with controls (325). It is possible that some of the negative studies did not image the bulb, one of the earliest sites of thickening (328).

The DCCT/EDIC study included cIMT measures at the start of EDIC follow-up in 1994–1996 and again in 1998–2000 (329). Among persons in the intensive group, cIMT progression in EDIC years 1–6 was significantly lower than among the conventional group (329,330), but change in years 6–12 was similar between the treatment groups (330). This finding indicates that A1c is clearly related to cIMT, but perhaps on a time course different than for other diabetes complications, most of which remained significantly lower in the intensive group over the full follow-up period. A German study showed that cIMT progression over 4 years was predicted by baseline BMI, A1c level, and systolic blood pressure (331).

Type 2 Diabetes. The largest studies conducted of cIMT to date in youth with type 2 diabetes are from Cincinnati, Ohio (332,333). Youth with type 2 diabetes had significantly thicker cIMT for all segments than lean controls and a thicker bulb and common carotid than obese nondiabetic controls (332). Older age, male sex, and higher A1c were all associated with thicker cIMT (334). In addition, higher diastolic blood pressure and LDL cholesterol were associated with thicker internal cIMT. In a study by Gungor *et al*. of 20 youth with type 2 diabetes compared with lean and obese nondiabetic controls, no differences in cIMT were seen (322), though the small sample size may have resulted in a type 2 error.

Diabetes of both types commonly increases arterial wall thickness only a few years after diabetes onset and many years before clinical symptoms and events occur. Comparisons across types of diabetes are possible only in the Ohio studies, which used the same methods and laboratory. In those studies, youth with type 2 diabetes appear to have thicker arteries (332) than those with type 1 diabetes (328), but this comparison has not been directly analyzed to remove potential confounding.

Coronary Artery Calcification

Evaluation of the amount of calcium located in the coronary arteries measured by electron beam tomography or multi-slice detector computed tomography has become a well-established tool for predicting cardiovascular event risk in adults (335), independent of other measured risk factors (336). Because CAC prevalence is low in youth and rises sharply with age, few studies of young persons with short duration diabetes have been conducted.

Type 1 Diabetes. In a clinic-based study of 101 youth with type 1 diabetes age 17–29 years, with a minimum of 5 years of duration, Starkman *et al*. found the prevalence of CAC scores >0 to be 10.9% and higher in men than women. Smokers had a fivefold higher prevalence, but no association was seen with A1c, diabetes duration, BMI, or microalbuminuria, though the sample size was small (337). The Pittsburgh EDC study of progression of CAC scores found that traditional CVD risk factors and increasing BMI were associated with increasing CAC scores, but A1c was also not associated with progression (338). In Denver, Colorado,

the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study included >500 youth-onset type 1 diabetic persons with current age 20–55 years and a mean diabetes duration of 23 years (339). CAC prevalence was 2.1 times higher in men with type 1 diabetes than controls and 3.6 times higher among women, mirroring the excess cardiovascular risk among women with diabetes. The youngest group examined (age 20–29 years) had prevalences of 24% (males) and 14% (females). Progression of CAC showed a strong association with poor glycemic control, as well as with higher BMI and insulin dose (340). Longer CACTI follow-up has shown that CAC progression is also related to lower HRV (341). CAC was measured in 86% of surviving DCCT/EDIC participants 7–9 years after DCCT closeout (342). Prevalences of CAC >0 and >200 Agatston units were 31.0% and 8.5%, respectively. The intensive treatment group had significantly lower geometric mean CAC scores and lower prevalence of CAC >0 in the primary prevention cohort, but not in the secondary prevention cohort, a result that was primarily driven by A1c differences between the cohorts. Prevalence of CAC >200 was significantly lower among the intensively treated group when the two cohorts were combined. Older age, male sex, smoking, higher albumin excretion rate, larger waist-hip ratio, hypertension, and higher A1c level during DCCT all were independently associated with higher CAC score up to 9 years post-trial.

Not all studies of CAC in persons with type 1 diabetes have found a significant role for elevated A1c levels (337,343). The failure to identify a role for A1c in observational cohorts may be due to a wider range of risk factors present, compared to the DCCT, which excluded participants with hypertension and hypercholesterolemia and which may have made it easier to detect an effect of A1c. The observation of an effect in the primary prevention cohort, with a mean diabetes duration of only 2.5 years prior to the DCCT, also suggests that excellent control of A1c should be established as early as practicable.

Type 2 Diabetes. No studies have explored CAC in youth with type 2 diabetes.

MORTALITY

Mortality studies in North American youth with diabetes are based on three primary cohorts: the Pittsburgh, Pennsylvania, EDC (Pittsburgh Children's Hospital) and Allegheny County Pennsylvania registry data (344,345,346,347), the Chicago Diabetes Registry of minority youth (348,349), and the Pima Indian study (232). The Pittsburgh information is based on cohorts of youth-onset type 1 diabetic cases followed from 1965 to 2007, the Chicago data include largely minority youth with a mixture of presumed type 1 and type 2 diabetes from 1985 to 2000, whereas the Pima Indian study includes individuals with youth-onset type 2 diabetes. Data are summarized in Table 15.7.

Type 1 Diabetes

The series of mortality studies from the Pittsburgh area spans many years and multiple reports (344,345,346,347). The 2001 report from the population-based registry calculated rates and standardized mortality ratios (SMRs) at 20 years of diabetes duration. Overall, males with type 1 diabetes and age of onset <18 years were 2.2 times more likely to die than nondiabetic males in the same area; females were 7.8 times more likely to die (344). African Americans had higher mortality rates than non-Hispanic whites. These studies also showed that total mortality at 20 years duration of diabetes was declining among those with more recent onset. A subsequent Pittsburgh study (345) added cases from Children's Hospital to the County registry, increased the degree of death ascertainment (to 94%), and provided cause of death information. At 20 years duration of diabetes, persons with youth-onset type 1 diabetes had mortality rates (per 100,000 person years) of 101 for acute complications, 328 for chronic complications, and 81 for nondiabetes causes, with 23 from unknown causes. African Americans had significant excess mortality from acute complications (hazard ratio 4.9) compared to non-Hispanic whites. Total and cause-specific mortality decreased with later years of diabetes onset (1975–1979 vs. 1965–1969) (345). Results from Allegheny County (346) that extended the duration of follow-up to 30 years showed that compared with nondiabetic controls, persons with youth-onset type 1 diabetes had a 12.9-fold excess of CVD mortality, 104.3-fold excess of renal deaths, and 41.2-fold excess mortality from acute infections (346). The Pittsburgh EDC followed their cohort diagnosed at age <17 years for 30–60 years and estimated life expectancy by cohort of diabetes onset (347). For the cohort with type 1 diabetes onset in 1950–1964, life expectancy at birth was only 53.4 years. However, in the most recent cohort (1965–1979), life expectancy at birth had increased to 67.2 years, a gain of almost 14 years. The authors noted that these updated data should be used for patient counseling, since much of the older data are too pessimistic. Changes in treatment for diabetes, dyslipidemia, and hypertension likely have led to much of this improvement.

Similar findings, with shorter duration of follow-up, were noted by two Chicago studies. After short follow-up, the initial mortality results for type 1 diabetes included only SMRs, since there were only 30 total deaths (348). Rates from the comparable nondiabetic population were used to estimate the expected number of deaths and were compared to the observed number. The resulting SMRs were 1.3 for non-Hispanic whites, 3.9 for African American youth age 0–24 years, and 3.5 for Hispanics for all types of diabetes combined. After 7.8 years of follow-up (through 2000), the estimated mortality rate for type 1 diabetes was 237 per 100,000 person-years, slightly lower than the rate among youth with presumed type 2 diabetes, estimated at 288 per 100,000 person-years (349).

The largest study of lifetime mortality among persons with youth-onset type 1 diabetes was conducted in the United Kingdom and was based on a cohort of 23,752 youth from multiple participating clinics (350,351). Focusing on the youth

who died at ages ≤9 years and 10–19 years, all cause SMRs for males were 2.5 and 2.3, respectively, whereas for females, they were 3.8 and 3.6, respectively (350). The early excess of ischemic heart disease mortality was assessed in a follow-up study among youth dying at age 10–39 years (351). Among men, the SMRs for ischemic heart disease were 17.0 (age 10–19 years), 11.8 (age 20–29 years), and 8.0 (age 30–39 years). Among women, the SMRs were much higher: 27.8, 44.8, and 41.6 for the three age groups, respectively (351). This result highlights the excess female heart disease mortality at very young ages among youth with type 1 diabetes.

Other studies from population-based registries in Europe are consistent, showing twofold to fivefold excess mortality in youth-onset type 1 diabetes (164,352,353,354). A Finnish study showed declining SMRs in youth with type 1 diabetes and onset at age <15 years in more recent cohorts (SMRs 3.5 in 1970–1974 to 1.9 in 1985–1989) (354). In contrast, youth with onset at age 15–29 years had increasing SMRs in more recent cohorts (from 1.4 to 2.9) propelled by increases in death rates from acute complications over time, with no change in mortality rates from chronic complications and with increases in alcohol and suicide-related causes (354).

Type 2 Diabetes

Studies of mortality among youth-onset type 2 diabetes remain uncommon. Among Pima Indian youth with onset of type 2 diabetes at age <20 years, mortality rates were 2.1 times higher at age 20–54 years than among persons with diabetes onset at age ≥20 years (1,540 vs. 730 per 100,000 person-years respectively). Compared with nondiabetic persons, age-sex-specific mortality rates in those with youth-onset type 2 diabetes were 3.1 times as high, whereas mortality rates in those with adult-onset type 2 diabetes were only 2.1 times as high (232). The longer duration of diabetes in youth-onset persons was largely responsible for the excess age-specific mortality. As more youth with type 2 diabetes age into young adult and middle ages, it is likely that similar patterns of excess mortality will occur due to the early onset and longer duration of diabetes. Youth with presumed type 2 diabetes in Chicago had slightly higher mortality rates after 7.8 years of follow-up (288 per 100,000 person-years) than youth with presumed type 1 diabetes (237 per 100,000 person-years) (349). In Sydney, Australia, the cumulative mortality after 21 years of follow-up was 11.0% for youth with type 2 diabetes, higher than the 6.8% seen in youth with type 1 diabetes (p=0.03) (248).

All Types of Diabetes

Saydah *et al.* estimated the trend in mortality rates for all types of diabetes among youth age 0–19 years in 1968–2009 in the United States (Figure 15.5,

TABLE 15.7. Mortality Studies Among Persons With Youth-Onset Diabetes

REFERENCE	POPULATION; YEARS	DURATION OF FOLLOW-UP, METHOD	MORTALITY OUTCOME	COMMENTS
Type 1 diabetes				
348	Chicago, IL; age 0–24 years at death; census denominator and local mortality rates; 30 deaths; 1987–1994	No follow-up; deaths identified from death certificates	SMR Non-Hispanic white 1.3 Non-Hispanic black 3.9 Hispanic 3.5	Significant excess SMR for black and Hispanic youth; uncertain completeness of death ascertainment.
344	Pittsburgh, PA, Allegheny County population-based registry; 1,075 T1 cohort age <18 years at diagnosis in 1965–1979; follow-up through 1998; 93% white, 7% black; 1965–1999	Vital status by local confirmation and National Death Index; cause of death adjudicated by panel	Mortality rate/10^5 person-years at 20 years of diabetes duration Diagnosis year 1965–1969 457 1970–1974 345 1975–1979 229 Race White 335 Black 508 SMR at 20 years duration All 3.7 Men 2.2 Women 7.8	90.4% ascertainment of vital status; significant decline in mortality for cohorts diagnosed more recently (p<0.01); no difference by sex.
345	Pittsburgh, PA, Allegheny County population-based registry and Children's Hospital registry with cause of death; 1,261 T1 youth age <17 years at diagnosis in 1965–1979; follow-up through 1998	Vital status by local confirmation and National Death Index; cause of death adjudicated by panel	Mortality rate/10^5 person-years at 20 years of diabetes duration Cause of death All 533 Acute diabetes 101 Chronic diabetes 328 Nondiabetic 81 Unknown 23 Diagnosis year 1965–1969 818 1970–1974 435 1975–1979 250	93.9% ascertainment of vital status; 79% with known cause of death; black youth had significantly higher mortality from acute complications (HR 4.9, 95% CI 2.0–11.6) than white youth; not for other causes; mortality decreased for each period of onset and for all causes. Rates include those who died at diabetes onset.

Table 15.7 continues on the next page.

TABLE 15.7. (continued)

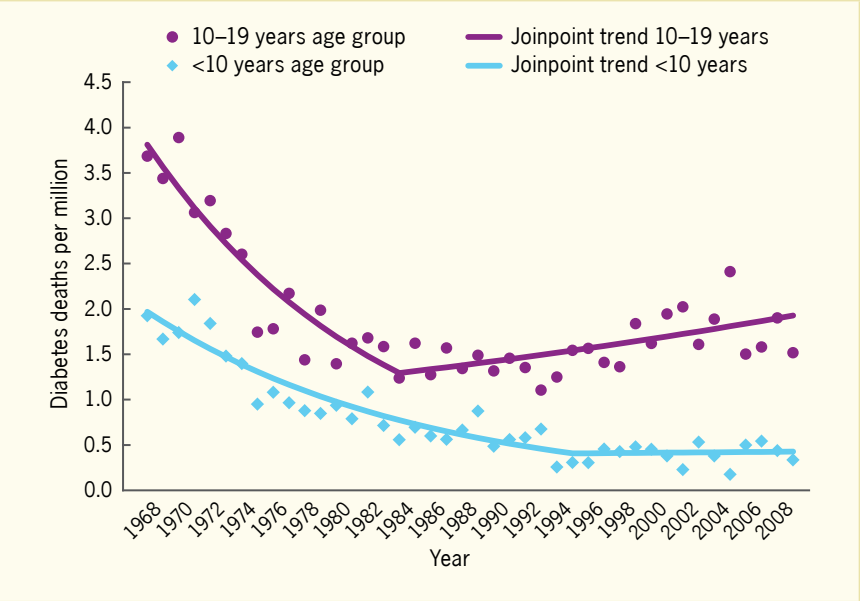
REFERENCE	POPULATION; YEARS	DURATION OF FOLLOW-UP, METHOD	MORTALITY OUTCOME	COMMENTS
346	Pittsburgh, PA, Allegheny County population-based registry, N=1,043; 279 deaths; 34,363 person-years of follow-up; T1 cohort age <18 years at diagnosis in 1965–1979; follow-up through 2007	29–43 years; mean diabetes duration 32 years; National Death Index used to locate deaths; cause of death adjudicated by panel	Mortality rate/10^5 person-years at 30 years of diabetes duration Diagnosis year 1965–1969 ... 800 1970–1974 ... 676 1975–1979 ... 531 SMR at 30 years of diabetes duration Cause of death CVD ... 12.9 Renal ... 104.3 Infection ... 41.2	97% ascertainment of vital status; cause of death by record review and adjudication; females and blacks had higher rates than males and whites.
347	EDC (Pittsburgh, PA) cohort; N=933; 145 deaths; age <17 years at diagnosis in 1950–1980; followed through 2009	Estimated life expectancy by cohort of diagnosis	Life expectancy (years) Diagnosis cohorts: 1950–1964 / 1965–1980 / 1965–1979 Birth ... 53.4 / 68.8 / 67.2 Age 50 ... 26.7 / 29.2 / 31.1	Hospital-based but representative of the population-based Allegheny County registry.
248	Sydney, Australia, Royal Prince Alfred Hospital clinical cohort; 470 T1 with age of onset 15–30 years; mean diabetes duration 14.7 years; mean age of onset 25.1 years; 1986–2011	Australian National Death Index; all cause through 2011, cause of death through 2008; >23 years of mortality follow-up	Case fatality rate ... 6.8%	Not population-based; serves large geographic region of Sydney, Australia; A1c mean 8.1%.
Type 2 diabetes				
232	Pima Indians, AZ; T2 persons with age of onset <20 years; 20–54 years at death; N=1,856; 233 deaths; 1965–2002	Death verified from medical records, autopsy, and death certificates; maximum of 38 years follow-up; mortality rates for persons age 20–54 years	Mortality rates/10^5 person-years for age at death of 20–54 years Age of onset (years) <20 ... 1,540* 20–54 ... 730* * Age-sex-adjusted	Compared to nondiabetic persons, those with youth-onset diabetes were 3.1 times more likely to die; those with adult-onset diabetes were 2.1 times more likely to die; longer diabetes duration largely accounted for outcomes.
248	Sydney, Australia, Royal Prince Alfred Hospital clinical cohort; 354 T2 persons with onset from age 15–30 years; mean diabetes duration 14.7 years; mean age of onset 25.1 years; 1986–2011	Australian National Death Index; all cause through 2011, cause of death through 2008; >21.4 year mortality follow-up	Cumulative mortality ... 11.0%	Not population-based; serves large geographic region of Sydney, Australia; A1c mean 8.1%; cumulative mortality significantly higher than T1 (p=0.03); T2 deaths occurred at significantly shorter duration (mean 26.9 years vs. 36.5 years for T1 (p=0.01)); T2:T1 odds ratio 2.0 (p=0.003).
All types of diabetes				
349	Chicago Diabetes Registry, IL; 1,238 youth with age of onset <18 years; all types of diabetes; 7.8 years follow-up; 1985–2000	National Death Index, local follow-up; death certificates	Rate/10^5 person-years Age of onset (years) 0–9 ... 148 10–13 ... 381 14–16 ... 161 17 ... 1,526 Black ... 345 Hispanic ... 239 Presumed T1 ... 237 Presumed T2 ... 288	Not population-based; no time trend from 1985 to 2000; T1 and T2 diagnoses are "presumed" due to incomplete data for type of diabetes.
355	U.S. mortality rates for youth with diabetes (all types); 1968–2009	Annual mortality rates from diabetes as underlying cause on death certificate; denominator: U.S. Census	Rates per million (10^6) Age (years) at death: <10 / 10–19 1968–1969 ... 1.80 / 3.56 2008–2009 ... 0.39 / 1.71	Population-based; rates decreased by 78% among those age <10 years, and by 52% among those age 10–19 years; decrease in rates in 10–19-year-olds occurred prior to 1985; rates were level or rising slightly from 1985 to 2009; diabetes deaths likely under-ascertained using death certificate cause only.

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; CI, confidence interval; CVD, cardiovascular disease; EDC, Epidemiology of Diabetes Complications study; HR, hazard ratio; SMR, standardized mortality ratio; T1, type 1 diabetes; T2, type 2 diabetes.

SOURCE: References are listed within the table.

Table 15.7) (355). Among youth who died at age <10 years (essentially all with type 1 diabetes), the rates declined by 78% from 1968–1969 to 2008–2009. Among those age 10–19 years at death (primarily type 1 diabetes, but some with type 2 diabetes), rates fell by 52% over the same period. In this older age group, mortality rates declined prior to 1985 and remained level or rose slightly until 2008–2009 (355). The reasons for this pattern are unknown.

FIGURE 15.5. Annual Death Rates From Diabetes Per 1 Million Youth, by Age, U.S., 1968–2009



Based on diabetes as underlying cause of death, using International Classification of Diseases (ICD) codes as follows: for years 1968–1978, ICD-8 codes 250.0 or 250.9; for years 1979–1998, ICD-9 codes 250.0–250.9; for years 1999–2009, ICD-10 codes E10–E14.

SOURCE: Reference 355

CONCLUSIONS AND FUTURE DIRECTIONS

Although diabetes is one of the most prevalent severe chronic diseases of childhood, many gaps remain in understanding the epidemiology of diabetes in youth. The relatively recent occurrence of type 2 diabetes in youth has underscored that no standard case definitions exist for epidemiologic research or surveillance of pediatric diabetes. In addition, childhood type 1 diabetes has been increasing worldwide, and the reasons for this increase are not known. Few comprehensive population-based studies of diabetes according to type of diabetes in young people of diverse racial or ethnic backgrounds exist in the United States. Efforts directed at surveillance of diabetes in youth should not only continue but expand because of its increasing public health importance.

At the beginning of the 21st Century, several decades of increased risk and younger age at onset have occurred for both type 1 and type 2 diabetes. Projections indicate that these trends will worsen if the causes of diabetes are not rapidly identified and preventive strategies begun (356). Such strategies will likely require both individual, clinically based approaches and a much broader population initiative, targeting social and environmental factors that likely operate very early in life to alter energy balance, program the immune system, or promote beta cell failure.

The changing disease pattern also means that young people with either type 1 or type 2 diabetes will have a longer duration of exposure to an altered metabolic milieu, which may substantially increase the risk of chronic microvascular and macrovascular complications. The development of elevated levels of cardiovascular risk factors and preclinical cardiovascular disease among youth with diabetes and the potential future impact on morbidity and mortality pose special challenges. Growing evidence suggests an increased risk of diabetes-related chronic complications in young people with type 2 diabetes compared with those with type 1 diabetes. However, large-scale translational and epidemiologic studies in youth with diabetes are lacking, primarily due to the lack of common standardized protocols and validated surrogate endpoints that can be compared across studies.

The increasing number of young people with diabetes, coupled with the need for high-quality disease management, will further increase the already high cost of diabetes and may have a devastating effect on health care costs (356,357). Increasing understanding of the multifactorial etiology of childhood diabetes and its complications will hopefully translate into improved quality of life for youth with diabetes and will ultimately lead to the successful prevention of diabetes. The challenges are large for science and public health, but the cost of not proceeding urgently will be truly immense.

LIST OF ABBREVIATIONS

A1c. . . . . .glycosylated hemoglobin
ACR . . . . . .albumin:creatinine ratio
ADA . . . . . .American Diabetes Association
AER . . . . . .albumin excretion rate
Apo B. . . . . .apolipoprotein B
BMI . . . . . .body mass index
CAC . . . . . .coronary artery calcification
CACTI . . . . . .Coronary Artery Calcification in Type 1 Diabetes study
CAN . . . . . .cardiac autonomic neuropathy
CI . . . . . .confidence interval
cIMT. . . . . .carotid (artery) intima media thickness
CVD . . . . . .cardiovascular disease
DAISY. . . . . .Diabetes Autoimmunity Study in the Young
DCCT . . . . . .Diabetes Control and Complications Trial
DIAMOND . . . .Diabetes Mondiale project
DIPP . . . . . .Diabetes Prediction and Prevention study
DKA . . . . . .diabetic ketoacidosis
DPN . . . . . .diabetic peripheral neuropathy
EDC . . . . . .Epidemiology of Diabetes Complications study
EDIC . . . . . .Epidemiology of Diabetes Interventions and Complications study
ESRD . . . . . .end-stage renal disease
GADA. . . . . .glutamic acid decarboxylase autoantibody
HDL . . . . . .high-density lipoprotein
HLA . . . . . .human leukocyte antigen
HNF . . . . . .hepatocyte nuclear factor
HRV . . . . . .heart rate variability
IA-2A . . . . . .insulinoma associated-2 autoantibodies
IAA. . . . . .insulin autoantibody
ICA. . . . . .islet cell autoantibody
IS . . . . . .insulin sensitivity
LDL . . . . . .low-density lipoprotein
NHANES . . . . .National Health and Nutrition Examination Survey
NIDDK . . . . . .National Institute of Diabetes and Digestive and Kidney Diseases
NIH . . . . . .National Institutes of Health
OR . . . . . .odds ratio
PWV. . . . . .pulse-wave velocity
RRR . . . . . .relative risk reduction
SEARCH . . . . .SEARCH for Diabetes in Youth study
SMR. . . . . .standardized mortality ratio
TEDDY . . . . . .The Environmental Determinants of Diabetes in the Young study
TODAY . . . . . .Treatment Options for Type 2 Diabetes in Adolescents and Youth (trial)
TRIGR. . . . . .Trial to Reduce IDDM in the Genetically at Risk
WDRS . . . . . .Wisconsin Diabetes Registry Study
WESDR . . . . . .Wisconsin Epidemiologic Study of Diabetic Retinopathy
ZnT8A. . . . . .zinc transporter 8 antibody

CONVERSIONS

Conversions for A1c, cholesterol, glucose, and triglyceride values are provided in *Diabetes in America Appendix 1 Conversions*.

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DUALITY OF INTEREST

Drs. Dabelea, Hamman, and Knowler reported no conflicts of interest.

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