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Twenty years of pediatric diabetes surveillance: what do we know and why it matters

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Abstract

SEARCH for Diabetes in Youth (SEARCH) was initiated in 2000 as a multicenter study to address major gaps in the understanding of childhood diabetes in the United States. An active registry of youth diagnosed with diabetes at age <20 years since 2002 assessed prevalence, annual incidence, and trends by age, race/ethnicity, sex, and diabetes type. An observational cohort nested within the population-based registry was established to assess the natural history and risk factors for acute and chronic diabetes-related complications, as well as the quality of care and quality of life of children and adolescents with diabetes from diagnosis into young adulthood. SEARCH findings

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Competing interests

The authors declare no competing interests.

Disclosure

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC and the National Institute of Diabetes and Digestive and Kidney Diseases.

have contributed to a better understanding of the complex and heterogeneous nature of youth-onset diabetes. Continued surveillance of the burden and risk of type 1 and type 2 diabetes is important to track and monitor incidence and prevalence within the population. SEARCH reported evidence of early diabetes complications highlighting that continuing the long-term follow-up of youth with diabetes is necessary to further our understanding of its natural history and to develop the most appropriate approaches to primary, secondary, and tertiary prevention of diabetes and its complications. This review summarizes two decades of research and suggests avenues for further work.

Graphical abstract

We provide a summary of the design and methods used and an overview of major findings since the inception of the SEARCH for Diabetes in Youth Study in 2000. These include a summary of the risk, burden, and prognosis of diabetes diagnosed under the age of 20 years, with an emphasis on the disparities that were identified over these years. We also summarize morbidity and mortality information; patterns of, and barriers to, care of diabetes in youth; behavioral and social correlates; issues related to sustainable surveillance; and what the increase in young adults with diabetes who become parents implies.

Keywords

type 1 diabetes; type 2 diabetes; youth; surveillance; epidemiology; health disparities

Introduction

At the start of the 21st century, important gaps existed in the understanding of diabetes in youth under 20 years of age. Some of these gaps included sparse and incomplete incidence and prevalence data by type of diabetes, age, sex, and race/ethnicity; the uncertainty of whether the natural history of type 2 diabetes (T2D) was similar or different in youth compared with adults; whether an etiologic classification of childhood diabetes could be developed; the burden and risk factors for diabetes-related early complications; and the quality of health care and quality of life of youth with diabetes. In addition, data on demographics, social determinants of health, and patient-reported outcomes, including race and ethnicity, income, education, health insurance, geographic location, neighborhood characteristics, healthcare utilization, diabetes education, and others, were largely unknown on a population basis for youth with diabetes and their families.

The SEARCH for Diabetes in Youth (SEARCH) study was initiated in 2000 with funding from the Division of Diabetes Translation of the Centers for Disease Control and Prevention (CDC) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) to address these gaps and respond to emerging issues in the field of youth onset diabetes. The study was funded in 4–5-year grant cycles from 2000 ending in September 2020, a period of approximately 20 years.

We provide here a summary of the design and methods used and an overview of major findings since inception. These include a summary of the risk, burden, and prognosis of

diabetes diagnosed under the age of 20 years, with an emphasis on the disparities that were identified over these years. It also summarizes morbidity and mortality information; patterns of, and barriers to, care of diabetes in youth; behavioral and social correlates; issues related to sustainable surveillance; and what the increase in young adults with diabetes who become parents implies. This paper provides a thorough update from a prior publication [1].

Design of SEARCH

Populations

One of the major goals of the study was to identify all youth with new-onset (incident) diabetes of any type (type 1 diabetes (T1D), T2D, and other types),[2] except for gestational diabetes, diagnosed from 0 to 19 years of age, and to conduct periodic prevalence surveys to assess the burden of diabetes in the areas under study. Phase 1 (2000–2005) and 2 (2005–2010) included six recruitment centers: four geographic-based sites based in Ohio (eight counties, including Cincinnati, OH); the entire state of Colorado; five counties around Seattle, Washington; the entire state of South Carolina; and membership sites: two health plan–based sites in Hawaii and Southern California (health plan enrollees from one plan in seven counties); and under the direction of Colorado and in coordination with the Indian Health Service, American Indian reservation–based populations in Arizona and New Mexico. Phases 3 (2010–2015) and 4 (2015–2020) continued with five of the six original centers (excluding Hawaii). (Fig. 1)

Study components

SEARCH brought together multiple components relevant to youth-onset diabetes research: an active surveillance registry component (Fig. 2 top) to assess trends in incidence and prevalence. In addition, a separately funded observational cohort study was funded by NIDDK and CDC that provided for two additional follow-up visits on ~3000 youth with T1D and T2D[3] (Fig. 2, bottom).

Registry

In the geographic centers, the registries conducted active surveillance in the individual study areas by developing a network of endocrinologists (pediatric and adult), other high volume practices, hospitals, and health systems. These networks reported from one to four or more times per year to each geographic center registry all individuals with probable diabetes using administrative information. In the membership sites, individuals with diabetes were identified from electronic health records and reporting by endocrinologists along with chart reviews. All registries removed duplicate records, produced a listing of all unduplicated persons with diabetes, and conducted chart reviews to verify the presence of physician-diagnosed diabetes and other eligibility criteria (eligible residence in the study area, age <20 years at diagnosis, and noninstitutionalized) and to identify demographics and characteristics, such as diabetic ketoacidosis (DKA), within the first 6 months of diabetes. These activities were conducted under HIPAA waivers from the responsible institutional review boards.

To estimate incidence for a given year required collecting data from the network for longer periods of time, since an individual with newly diagnosed diabetes, especially T2D, may not first appear at a network members practice until well after diagnosis. An analysis of time from diagnosis to case registration showed that over 95% of all detected cases could be identified within 30 months of the end of the diagnosis year [4]. Thus, even though SEARCH was funded through 2020, incidence results are incomplete for 2019–2020 at this writing.

During 2002–2015, among 69,457,475 youth at risk for diabetes, SEARCH identified 14,638 youths with incident T1D and 3916 with incident T2D [5]. On the basis of the capture–recapture analysis [6, 7], there was a 98–99% completeness of ascertainment of cases of T1D and 92–97% for T2D.

With physician or health system permission, eligible persons were sent a brief questionnaire, and attendance was requested at a baseline in-person research visit to collect biochemical, genetic, and clinical data, which was conducted under informed consent or assent.

Population denominators

The geographic-based sites used race-bridged postcensal estimates of the nonmilitary, noninstitutionalized midyear populations in the center catchment areas as denominators to represent the population at risk. Health plans used end-of-year membership rolls, and Indian Health Service beneficiary rolls provide American Indian site denominators. The surveillance population was similar to the U.S. youth population with respect to the distribution of race/ethnicity, age, household income, and parental education [7]. The population under yearly surveillance for incident cases was approximately 5.5 million children <20 years of age, comprising about 4.9% of the U.S. population <20 years [8]. Approximately 3.5 million children <20 years of age were under surveillance in 2001, 2009, and 2017 for prevalence, owing to smaller areas of surveillance in Colorado and South Carolina than for incidence.

Cohort study

The cohort study was developed to understand risk factors for acute and chronic complications, to estimate the burden of such complications as they differed by duration, age, sex, and race/ethnicity, and to explore the processes of care and quality of care received by participants. Youth with a baseline in-person visit in 2002–2006, 2008, 2012, and 2016, and at least 5 years of duration by the time of the cohort visit were invited to participate [3]. Of registered cases, 39.6% participated in the baseline in-person visit [3] and 64.2% of those with a baseline visit had a cohort visit [3]. Those with a baseline visit were similar to all registered cases on multiple sociodemographic and biological parameters [7].

Study findings

The changing landscape of pediatric diabetes in the United States

Historical context.—From the 1960s through the mid-1990s, worldwide reports suggested that the incidence of T1D was increasing 2–4% each year, with earlier onset of diagnosis [9]. T1D was primarily described as a condition occurring among non-Hispanic

White youth. However, few population-based data existed in the United States to monitor trends in incidence, age at onset, or racial and ethnic distribution of incident T1D cases.

Initial case reports of youth-onset T2D cases emerged toward the end of the 20th century, coinciding with an increase in the prevalence of obesity in youth from 5% in the early 1970s to 14% by the end of the 1990s. Early studies monitoring trends in T2D in youth were limited to Native American communities [10, 11] or were clinic-based studies [12].

With the initiation of SEARCH, population-based estimates of incidence, prevalence, and trends in incidence and prevalence across time for youth-onset T1D and T2D, became possible. To date, nearly 30,000 cases of both incident and prevalent youth-onset diabetes have been registered. Data collected on these registered cases have informed our understanding of the changing landscape of youth-onset diabetes for nearly 20 years.

Disparities in the incidence of youth-onset T1D and T2D.—Initial (2002–2006) population-based estimates of youth-onset diabetes incidence (number of new cases per population) demonstrated significant racial and ethnic disparities. The incidence of T1D peaked among 10- to 14-year-olds. While few cases of T2D were identified among those less than 10 years, the incidence of T2D among non-Hispanic black, Asian and Pacific Islander, and American Indian populations for 10–14 years was greater than T1D. The higher incidence of T2D compared with T1D was observed among 15- to19-year-olds for every group except non-Hispanic Whites.[3] This disparity has persisted across time, with most recent reports demonstrating an overall higher incidence of T2D as compared with T1D in youth from racial and ethnic groups of color across ages 10–19 years [5].

Within diabetes type, surveillance of trends has demonstrated a marked increase in the incidence of both T1D and T2D. Overall, across the period 2002–2015, a 1.9% annual increase in T1D and a 4.8% annual increase in T2D incidence was observed. However, this increase has been experienced disproportionately among certain population groups. In T1D, non-Hispanic Blacks, Hispanics, and Asian/Pacific Islanders experienced the highest annual percent change increase (2.7, 4.0, and 4.4%/year, respectively) as compared with non-Hispanic Whites (0.7% increase/year). For T2D, the highest increase in incidence was observed among Asian and Pacific Islander youth, at 7.7%/year, as compared with 6.5%/year for Hispanics, 6.0%/year for non-Hispanic Blacks, 3.7%/year for Native Americans, and no significant change for non-Hispanic White youth (Fig. 3) [5].

Disparities in the prevalence of youth-onset T1D and T2D.—Surveillance of population-based prevalence (number of total cases existing at a point in time) is critical to monitoring population burden and disparities and informing the allocation of public health resources. In 2001, when first estimates of population-based prevalence of youth T1D and T2D were reported from SEARCH, T1D accounted for 90% of all diabetes cases among non-Hispanic Whites. For Native American youth, T2D accounted for the highest proportion of diabetes cases observed. In 2001, accounting for the race/ethnicity and sex distribution in the United States, it was estimated that ~154,000 youth were living with diabetes in the United States [13].

Prevalence of both T1D and T2D has increased across all racial and ethnic groups from 2001 to 2017, with the greatest increases observed among non-Hispanic Whites and non-Hispanic Blacks for T1D and non-Hispanic Blacks, Asian/Pacific Islanders, and Hispanics for T2D (Fig. 4). While the overall prevalence of T1D remains higher than T2D under the age of 20 years, the change in prevalence across this period for T2D was nearly double that of T1D (0.3/1000 to 0.7/1000 for T2D and 1.5/1000 to 2.2/1000 for T1D)[14]

Projections for youth-onset T1D and T2D burden.—The increasing trend in the incidence and prevalence of youth-onset diabetes is of significant concern, but perhaps most concerning is the disparity between racial/ethnic groups. With the trends noted above, coupled with the shift in the landscape of the demographic distribution of the U.S. population toward a more racially and ethnically diverse population, the public health burden of youth-onset diabetes will likely continue to grow. By 2050, it is estimated that as many as 600,000 youths <20 years of age will be living with T1D, at a prevalence of 5.2 cases/1000 youth <20 years of age. An estimated ~84,000 youth, aged 10–19 years, will have T2D, at a prevalence of 0.8 cases/1000 youth [15].

Disparities in morbidity and mortality associated with youth-onset diabetes.—Disparities in health outcomes by socioeconomic characteristics have been ingrained in U.S. society for centuries but recently have come to the forefront of public awareness in the past 40–50 years. These inequalities are reflected in all chronic illnesses, and despite attempts to level the playing field in pediatric health care, outcomes in youth onset diabetes are no exception. Moreover, while the incidence of diabetes-related complications has declined over the past 10 years in older adults, rates of major adverse cardiovascular events, amputation, and end-stage kidney disease have risen among younger age groups (18–44 years)[16]. Identifying disparities in morbidity and mortality associated with youth-onset diabetes has been a primary aim of the SEARCH Study since its inception.

Acute complications: diabetic ketoacidosis (DKA) and severe hypoglycemia.—SEARCH data were used in a multinational study of trends in DKA at diabetes diagnosis occurring from 2006–2016. While the combined prevalence of DKA was 29% (95% CI: 29–30%) for all nations, the United States fell into the higher range at 36% (95% CI: 35–38%), and was one of the few countries to have a rising trend in DKA at diagnosis [17]. Sociodemographic factors associated with increased risk for DKA at diagnosis in the United States included minority race/ethnicity (RR 1.14; 95% CI: 1.06–1.22) and age <5 years compared with >15 years (RR 1.23, 95% CI: 1.13–1.35). Although HbA1c levels one year after diagnosis were similar, those with DKA at presentation had a worse glycemic trajectory, being 0.16% per year higher than those without DKA at presentation [18]. Moreover, Black race, Hispanic ethnicity, and low-income families not only had a higher risk of DKA at diagnosis but also a higher risk for worsening glycemic status, independent of DKA at diagnosis [19].

Severe hypoglycemic events, defined as very low blood sugar requiring help from another person, occurred over a 6-month time period in approximately 7% of youth with T1D and 2.6% of youth with T2D [20]. While there is a wide range in frequency of severe hypoglycemia, the median frequency was one event over 6 months for both T1D and T2D.

Among individuals experiencing severe hypoglycemia, emergency medical services were contacted for 40% of youth with T1D and 14% of youth with T2D. Temporal trends were not examined.

Chronic early complications and comorbidities.—In the exploration of complications that occurred in persons with a short duration of diabetes (early complications), SEARCH characterized diabetes type according to likely etiology defined by the presence of diabetes autoantibodies and insulin resistance [21, 22]. While the type of diabetes reported by the provider was highly correlated with this etiologic type, there was 15–20% misclassification in both T1D and T2D.[7] The use of etiologic type is relevant in this era of increasing obesity, as autoimmunity and insulin resistance are likely to have differing pathogenic risk factors and mechanisms for the development of complications. For example, the magnitude of insulin sensitivity has been linked to albuminuria [23, 24] and arterial stiffness [25, 26].

The prevalence of early diabetes-related complications were reported among 1746 participants with T1D (mean age 18 years (SD 4); 76% non-Hispanic White) and 272 with T2D (mean age 22 years (SD 4); 26% non-Hispanic White) at a mean adjusted diabetes duration of 8 years and an average age of 21 years in both groups [3]. The age-adjusted prevalence of microvascular complications and macrovascular risk factors are shown in Table 1. With the exception of cardiac autonomic neuropathy, all other complication rates were higher in youth and young adults with T2D versus T1D, even after adjustment for sociodemographic factors. Additional adjustments for differences in clinical factors (especially the waist–height ratio) attenuated to non-significance the increased odds of arterial stiffness and hypertension, but not the increased burden of albuminuria, retinopathy, and neuropathy among individuals with T2D compared with their peers with T1D [3]. At an average age of 21 years and a mean of 8 years of disease duration, approximately 1 in 3 individuals with T1D and almost 3 out of 4 of those with T2D had at least one microvascular complication or cardiovascular comorbidity. [3] Early cardiovascular comorbidities were notably prevalent, and more so in youth-onset T2D: up to 14% of those with T1D had cardiovascular autonomic neuropathy, hypertension, or arterial stiffness, compared with almost half (47%) of those with T2D [3]. Early evidence of cardiovascular disease was also apparent from increased carotid intima-media thickness relative to age-matched controls without diabetes [27, 28], particularly among those with worse glycemic control and/or higher BMI.

Approximately 6% of youth and young adults with T1D included in the cohort had multiple complications [29]. Specific types of vascular complications tended to cluster, particularly retinopathy with albuminuria and with arterial stiffness, suggesting shared etiologies. Cluster analysis of risk factors for multiple complications identified that T1D youth of non-White race/ethnicity, without health insurance, and with household income less than $50,000 per year were at the highest risk.

Mortality.—Among youth and young adults with an average diabetes duration of 5.3 years, crude mortality rates in T1D and T2D are 71 and 186 deaths per 100,000 person-years, respectively [30]. Leading contributors to the 26 deaths among individuals with T1D include

diabetes-related acute and chronic complications and accidents, whereas, in T2D, the majority of the 15 deaths were results of accidents or self-harm. Figure 5 depicts the overall and stratified standardized mortality ratios (SMR). Mortality ratios among individuals with T1D were comparable with the general population (SMR = 1.1, 95%: CI 0.7–1.6), while individuals with T2D had mortality over twice that of the general population (SMR = 2.4, 95% CI: 1.3–3.9). Females, non-Hispanic Blacks, and adolescents aged 15–19 years also had higher SMR.

Evidence for significant, adverse long-term disease-associated complications and comorbidities for youth-onset T2D is continuing to build. Youth diagnosed with diabetes 10–15 years ago are well into their third and even fourth decade of life, adding to the burden of diabetes in adults. Surveillance of complications and comorbidities will be important to determine how to mitigate risks and the burden of T2D. Surveillance of T1D complications and comorbidities will also be important given the increase in incidence and prevalence of T1D among racial and ethnic youth groups.

Barriers to quality pediatric diabetes care

Over the 20-year duration of the study, there have been opportunities to identify barriers and disparities in care and factors that lead to a successful transition from pediatric to adult care.

Access and process barriers.—Using questions from the National Longitudinal Study of Adolescent Health and Consumer Assessment of Healthcare Providers and Systems (CAHPS) surveys, sociodemographic factors were found to be associated with both access and process barriers to care.[31] Access barriers include having a regular provider, getting care thought to be needed, and cost of care. Processes of quality care include contextual care, that is, care that takes into account personal and family context, provider communication, and ability to obtain information. Greater barriers to accessing care and having a regular provider were seen in those with less parental education, utilizing public or health insurance, Black or Hispanic, and living in a single-parent household or ≥2 households.[31] Cost of care was a major barrier for all, except those on Medicaid.[31] Furthermore, Hispanic ethnicity and low parental education were associated with communication and contextual care barriers.[31] More than 80% of participants reported ≥1 barrier to care, most commonly cost, followed by obtaining information, communication, and contextual care.[31]

Both direct and indirect costs can pose significant barriers. Direct costs were examined by asking families of youth with T1D to report out of pocket expenses (OOPE) for diabetes medicines and supplies; mean cost was $65/month; 60% spent >$50/month, and 40% spent >$100/month.[32] Using an insulin pump or continuous glucose monitor was associated with higher OOPE.[32] These technologies often improve outcomes, but the financial cost can be burdensome and make them inaccessible. Lower household income, lower parental educational attainment, and being on public health insurance were associated with lower OOPE, as was seeing a pediatric endocrinologist relative to an adult endocrinologist or family practice provider.[32]

Disparities in care.—Disparities in diabetes care are multifaceted, including access, outcomes, and treatment regimens. Early in SEARCH, we reported on the association of

treatment regimen with sociodemographic measures, health insurance, and glycemic control in over 2,700 participants with T1D, mean age 13.2 years, and diabetes duration of 5 years. Insulin pump use was associated with better A1c in all but the youngest age group (Fig. 6).[33] Participants were more likely to be on an insulin pump or the basal–bolus regimen than multiple injection regimens if they were non-Hispanic White, had higher household income, and private health insurance.[33]

We subsequently examined factors associated with glycemic control within treatment regimens.[34] Those using an insulin pump were more likely to have good or intermediate control; however, the proportion with good control was very low at 14.4%, even for those on pump treatment (Fig. 7).[34] For those on insulin pumps, non-White race/ethnicity, living in ≥2 households, and public health insurance were ≥2 times more likely to have poor glycemic control.[34] For those using multiple daily injections (MDI), access, and process barriers (e.g., provider not spending enough time with family) were associated with poorer glycemic control.[34]

SEARCH assessed quality of care through self-reported receipt of testing, following American Diabetes Association pediatric guidelines, and associations with satisfaction with care. “Meeting criteria” was defined as ≥3 A1c measurements in the last year, blood pressure checks at each visit, and lipid screening, urine albumin/creatinine, and foot and eye exams in the prior 1–2 years. About 60% of participants met the criteria for A1c, 93% for blood pressure, 71% for lipid screening, 63% for albuminuria, 81% for an eye exam, and 64% for a foot exam.[35] Those meeting criteria had a mean A1c that was 0.28% lower than those not meeting screening criteria.[35] For each one-step increase in satisfaction, there was a greater likelihood of meeting criteria.[35] Most of these significant findings were attenuated after adjusting for race/ethnicity and socioeconomic factors, highlighting opportunities not only to improve the quality of care but also to address disparities in care.

Disparities in transition to adult care.—The transition from pediatric to adult diabetes care can be difficult for youth and young adults. In 185 youth with T1D who were ≥16 years old at the baseline visit, the mean age of transition from pediatric to adult diabetes care was 21.1 years[36]. Factors associated with leaving pediatric care were older age, less parental education, and higher A1c at baseline.[36] Higher A1c at baseline was associated with a lower likelihood of leaving pediatric care, highlighting the tendency of pediatric providers to retain individuals with greater psychosocial needs. Poor glycemic control was more common in those who left pediatric care. Most striking was race/ethnicity, with minority racial/ethnic groups 3.5 times more likely to have poor glycemic control relative to non-Hispanic White participants.[36]

Similar results were observed in young adults with T2D regarding the transition from pediatric to adult care. In 182 young adults with T2D who were in pediatric care when ˂18 years of age, 56% transferred to adult care by 25 years of age while 15% were receiving no care for their diabetes.[37] Older age, older age at diagnosis, and (unlike T1D) higher baseline A1c were all associated with leaving pediatric care. Males were more likely to have no care at follow up. Those with no provider or an adult provider were more than four times more likely to have poor glycemic control compared with those followed by a pediatric provider.[37]

Those with private health insurance were more likely to remain in pediatric care, whereas those on Medicaid or uninsured were more likely to have no care at follow up.[37]

SEARCH provided evidence that barriers to care exist, with >80% of SEARCH participants reporting at least one barrier.[31] It is incumbent on diabetes providers to follow excellent existing guidelines, to enhance patient and family satisfaction, and to address disparities on all levels—barriers to care, treatment, and outcomes. Successful transition from pediatric to adult care that ensures continuity of care and sustained glycemic control is essential. While our findings may represent the best-case scenario, as participants were sufficiently motivated to attend a study visit, participants sometimes reported no recent care, provider, or health insurance; and worrisome complications were observed in these individuals. There is a clear need to identify better strategies to improve the delivery of care and outcomes so that all youth and young adults with diabetes can live full and healthy lives.

Behavioral, psychosocial, and social correlates of pediatric diabetes

Behavioral correlates—nutrition and dietary behaviors.—Nutrition and dietary behaviors are major correlates of age at onset, glycemic control, and cardiovascular risk factors in pediatric diabetes from early life onward.

Early life factors.—Intrauterine exposure to maternal gestational or T2D (i.e., fetal overnutrition) was associated with a younger age at diagnosis of T2D.[38] Consumption of sugar-sweetened beverages or juice in infancy was associated with a younger age at diagnosis of T1D, particularly among those with the high-risk/susceptible genotype.[39] Higher fatty acid and leucine intake in the year after the diagnosis of T1D was associated with higher fasting c-peptide levels 1–2 years later, suggesting a protective effect of these nutrients on sustained beta-cell function.[40] Further, higher vitamin D levels in the first year post-diagnosis of T1D was associated with lower insulin resistance in cross-sectional analyses, even after adjustment for body mass index.[41]

Glycemic control.—Glycemic control and cardiovascular risk factors (obesity, dyslipidemia, hypertension) were improved with greater adherence to the Dietary Approaches to Stop Hypertension (DASH) diet;[42–44] greater intake of leucine, protein, and fatty acid intake;[45] and a lower intake of fructose,[46] trans-fatty acids,[47] diet beverages,[48, 49] sweetened beverages, eggs, potatoes, and high-fat meat.[50] Positive nutrition behaviors, such as counting carbohydrates[51, 52] and eating <5 times/day,[53] were associated with better glycemic control for both types of pediatric diabetes. All of these analyses were adjusted for insulin regimen and other key clinical and sociodemographic covariates, highlighting a potential benefit of dietary intake on HbA1c and cardiovascular risks above and beyond clinical treatment.

Populations at special risks.—Importantly, these findings highlighted subpopulations that were most likely to have suboptimal nutrition or dietary behaviors. Specifically, living farther from supermarkets, living closer to fast food outlets, having parent(s) with lower educational attainment, increasing age, and lower physical activity were associated with lower adherence to the DASH diet.[42, 44, 54] Participants who were male, non-White, older, or

from lower-income households had the highest intake of sugar-sweetened beverages,[55, 56] and were less likely to have dietary consumption patterns associated with better glycemic and cardiovascular profiles.[50] These data help explain some of the persistent disparities in pediatric diabetes management and specifically highlight the need to consider both individual- and community-level factors in dietary counseling for pediatric diabetes.

Screen time and smoking behaviors.—Other behaviors that are key to glycemic control and cardiovascular risk factors were screen time and smoking. Increases in daily screen time were associated with rising A1c levels for T1D and T2D and were associated with further elevations in triglycerides or LDL cholesterol for T1D.[57] Males, non-Hispanic Blacks, and Hispanics reported watching significantly more television than females and non-Hispanic Whites,[58] and thus may specifically warrant clinical attention and support for reducing screen time. Former and current tobacco users exhibited elevated cardiovascular risk factors compared with never users, with the most robust associations observed with dyslipidemia in T1D.[26] Up to 15% of SEARCH participants reported current tobacco use, with the highest use observed among those with T2D, of American Indian heritage, or from lower-income households.[59] Given the adverse impact of smoking on cardiometabolic health in this high-risk group, continued efforts to reduce smoking in pediatric diabetes patients is critical.

Psychological correlates.—Psychological correlates of glycemic control in youth-onset diabetes include depressive symptoms, quality of life, perceived weight status, unhealthy weight loss practices, and disordered eating behaviors. Among youth with T1D or T2D, elevated A1c levels were associated with more depressive symptoms and declining diabetes-related quality of life.[60–62] These associations were also higher among those who engaged in unhealthy weight loss practices or disordered eating behaviors to address their weight.[63, 64] Females with diabetes exhibited these adverse psychological states and behaviors more frequently than males, as did individuals who are older, are of non-White race/ethnicity, are overweight/obese, live in lower socioeconomic households, or have other comorbid conditions.[60–64] Given the negative association with glycemic control, it is important to provide mental health screening, especially to individuals with these sociodemographic characteristics, and ensure ongoing support for improved psychological states. These data further demonstrate that subgroups with already known disparities are particularly at risk of having complex barriers to glycemic control and confirm the need for comprehensive and integrated support from a diverse clinical care team.

Social correlates.—The incidence of T1D was highest in neighborhoods with a medium population density and lowest in neighborhoods with lower affluence,[65, 66] consistent with international studies,[67–69] suggesting that socioeconomic status–related lifestyles may potentially influence the etiology of T1D. By contrast, the incidence of T2D was highest in areas with low population density and rural classification,[70] which may be due to disparities in health-promoting built environments (e.g., limited access to healthy foods, fewer physical activity facilities, and reduced walkability).[71, 72] Indeed, participants living in neighborhoods with relatively lower supermarket density had higher body mass indices and waist circumferences.[54] Surprisingly, participants living farther from fast food outlets also

had significantly higher BMIs,[54] although this is likely due to the higher density of both supermarkets and fast food outlets in neighborhoods with greater population density. At the household level, 16% of SEARCH participants with T1D and 29% with T2D experienced food insecurity or limited availability of nutritionally adequate and safe food.[73] Food insecurity is associated with a nearly 1% increase in A1c levels in T1D, even after adjustment for socioeconomic indicators and health insurance.[74, 75] Participants with low or very low food security were more likely to be from households with lower affluence and more likely to be using insulin injections rather than an insulin pump.[74, 75] These results indicate that youth and young adults from disadvantaged households face multiple barriers to achieving glycemic control, with food insecurity specifically accounting for a notable elevation in A1c.

SEARCH has identified multiple social, behavioral, and psychological correlates linked to pediatric diabetes incidence, progression, and management (Table 2), the number of which further demonstrate the complexity of this disease and the comprehensive support required to manage it well. For children and adolescents who are still developing cognitively and emotionally, the burden is substantial and appears to grow as they transition through adolescence to adulthood. Males and females struggle with different psychosocial and behavioral components of diabetes, and individuals of minority race/ethnicity or lower socioeconomic status appear to face the most barriers to optimal social, behavioral, and psychological conditions. The development of effective strategies that target the behavioral, psychological, and social correlates is needed for both types of pediatric diabetes.

Research opportunities created by SEARCH

Continued surveillance of youth-onset diabetes

Continued surveillance of youth onset diabetes prevalence is critical to monitor and track disease burden and to inform public health resource allocation. Understanding trends in the incidence of disease can provide evidence of improvement in the environment or from policy changes aimed at improving risk once clinical trials have shown evidence of efficacy. With a high proportion of providers utilizing electronic health records for management of patient care, new opportunities have emerged for conducting surveillance of chronic disease. These approaches are not without limitations, as the data collected are for patient care, as opposed to research; thus misclassification and missing data are common challenges in working with these data. Still, newer methods for utilizing electronic health record data are emerging. Substudies at two sites showed that the use of search algorithms that used International Classification of Diseases - 9 (ICD-9) codes and limited chart review were potentially ways to use EHRs for surveillance [76–78]. An additional report showed that the use of ICD-10 codes significantly improved the identification of the type of diabetes [79]. SEARCH recently demonstrated the ability to ascertain cases of T1D and T2D through testing of a rule-based algorithm approach and multinomial regression approach applied to electronic health record data. For T1D, either approach yielded a sensitivity of >0.95 and specificity of >0.96 to detect true cases. For T2D, the rule-based method, combined with chart reviews, yielded a sensitivity and specificity of ≥0.91 [80]. The year of diagnosis, which is required to identify a new-onset case for annual incidence estimates is not generally available in administrative or

structured EHR data. In the attempt to identify the year of onset, youth (<20 years) with potential evidence of diabetes in 2017 (ICD code, elevated glucose or HbA1c, or DM medication) were identified from the inpatient and outpatient EHR data of three participating Children's Hospitals. All potential cases were chart reviewed to determine true diabetes status, type, and diagnosis date. Cases were restricted to those with diagnosis date and data post-2008 as a result of EHR limitations in earlier years. The use of the first ICD code identified in the EHR, and multi-criteria algorithms (using ICD code or elevated glucose, A1c, or medications) classified diagnosis year correctly 88.9% and 88.4% of the time, respectively, with significant improvement in later years of onset in the EHR.[81] Thus, it appears that the use of EHRs with a limited additional chart review in specific instances may be a cost-effective way to conduct surveillance.

Surveillance for youth onset diabetes is part of a robust registry system over long periods of time in much of Europe and Australia, but not in the U.S. SEARCH was not designed to be geographically or demographically representative of the United States though it enrolled a similar population [7]. In addition, record linkage is difficult in the United States with multiple health systems and payers. The SEARCH surveillance work over the past 20 years informed a new funding initiative, supported by the CDC and NIDDK, for surveillance of the burden of diabetes by type in children, adolescents, and young adults (Diabetes in Children And Young Adults (DiCAYA)). This new surveillance effort will be underway soon at several sites in the United States, including several prior SEARCH sites. However, the successor to SEARCH, DiCAYA, is also not designed to be representative. It is likely that significant geographic differences exist in both T1D and T2D in the United States, which could provide clues to the role of the environment in the etiology of diabetes. Whether every state needs a surveillance system depends on a number of factors: actual risk in the population; the prevalence of social and behavioral correlates summarized above; and the presence of enough evidence-based interventions that could reduce risks in the population such that surveillance could examine impact at a local, state, or regional level. We are clearly not at that stage for youth onset diabetes but identifying interventions that are scalable and linking population surveillance to areas that are introducing such interventions is an appropriate way to establish efficiency. There also has not been a tradition of linking population registries for youth onset diabetes to clinical care, yet many types of registries at hospitals or systems influence care regularly. Whether these two systems can converge with the advent of the EHR remains to be seen.

The future of offspring in the setting of parental diabetes

The rise in youth-onset T1D and T2D has resulted in a growing number of women and men entering their reproductive years with diabetes,[8, 82] with potential adverse impacts on pregnancy, perinatal, and offspring health outcomes.[83] Maternal diabetes triples the risk for major congenital anomalies,[84] and increases the risk for fetal macrosomia, shoulder dystocia, and neonatal respiratory disorders.[85–87] Poor glycemic control in early pregnancy is associated with spontaneous abortion and birth defects.[84] In most studies, adverse effects are similarly observed in both T1D and T2D.[88–92] Yet other maternal factors that contribute to adverse outcomes are more common among women with T2D, including overweight and obesity,[87] tobacco use,[93] chronic hypertension[88, 93], lower use of preconception care

services,[94] and late entrance into prenatal care.[95] Collectively, these data highlight the importance of managing risk factors for pregnancy complications before conception to facilitate optimal perinatal outcomes.

Offspring of women with diabetes may also exhibit impaired health trajectories from infancy onward. Many have elevated weight for length in infancy and childhood, especially when born large for gestational age.[96, 97] Others have relatively slower growth in infancy followed by accelerated growth in childhood, resulting in higher body weight as early as 5–7 years.[98, 99] Throughout childhood and adolescence, offspring of women with diabetes exhibit increased body size,[100, 101] more glucose intolerance,[101] and a higher prevalence of T2D[102] compared with unexposed offspring. They also have increased blood pressure,[103–106] inflammation and endothelial dysfunction,[105] dyslipidemia,[107] and a higher prevalence of metabolic syndrome.[108] While the postnatal environment and modeled health behaviors do contribute to transgenerational diabetes,[65, 66, 70, 109] intrauterine exposure to maternal diabetes is a major risk factor. Compared with siblings born before mothers developed T2D, siblings born after the mothers diagnosis had a greater BMI (2.6 kg/m^2) and were 3.6 times more likely to have T2D themselves by their early 20s.[110]

Paternal diabetes may also confer increased risk to offspring, although effects are less robust and not as clear as for maternal diabetes.[111] Offspring of fathers with diabetes may be smaller at birth,[112] but later exhibit increased body size, adiposity, metabolic disturbance, and T2D.[112–116] Genetic transmission of high-risk alleles for T1D, epigenetic effects on offspring gene expression, and the fathers influence on the postnatal environment and family practices are all potential mechanisms. Given the growing number of males with diabetes during their reproductive years, a better understanding of the specific influences of paternal diabetes on offspring health is warranted.

Notably, poor outcomes are not observed among all offspring of parents with diabetes, and there is substantial variability in the magnitude of risk conferred by diabetes status[100, 101, 117]. Neither genetics nor intrauterine environmental indicators (e.g., prenatal glycemic control or birthweight) fully explain the individual variability in offspring outcomes [118, 119]. Other postnatal factors are likely involved, but supporting evidence is currently limited. Among children of mothers with T1D in the Netherlands, the prevalence of overweight/obesity among offspring at 6–8 years was nearly three-fold higher in those whose mothers were currently overweight, [118] highlighting the potential for maternal health and modeled behaviors to modify the effect of intrauterine exposures. Similarly, among offspring exposed to maternal T1D or T2D, breastfeeding is associated with reduced obesity,[120, 121] and thus may be a strategy for improving outcomes in this high-risk population. Better diet and activity behaviors in offspring exposed to gestational diabetes have been associated with reduced body size and adiposity in childhood and adolescence;[122, 123] yet, similar evidence is not currently available for pregestational diabetes. Further research into the modifiable, postnatal factors that could mitigate risk could develop targeted interventions for the growing number of offspring born to parents with diabetes.

Aging with diabetes

The SEARCH cohort participants are now in their 20s and are exhibiting an increasing burden of cardiovascular-related complications and comorbidities. These trends are likely to worsen as participants transition into their 3rd and 4th decades of life, in parallel with the increasing prevalence of overweight/obesity in both T1D (~35%) and T2D (~90%) diabetes, [124] as well as dyslipidemia and smoking. [59, 124, 125]. Recent National Health and Nutrition Examination Survey (NHANES) data suggest that young adulthood is a vulnerable period for persons with diabetes: at a mean age of 36.4 years, with an average of 7.7 years of clinical diabetes duration, 29% had no health insurance, 22% had Medicaid-like plans, and only 65% reported having a usual place to receive care [126]. Moreover, young adults with diabetes had significantly elevated lipids and adiposity, poorer diet, and less physical activity, and were less likely to be treated for high cholesterol or hypertension than older adults with diabetes. The reasons for these troubling trends regarding diabetes in young adulthood are not clear. They may result from a more aggressive disease process among people with a younger age at onset of diabetes, for which increasing data are available, at least with respect to youth-onset T2D. [127] Alternatively, a combination of systemic, socioeconomic, healthcare access, transition from pediatric to adult care, limited health insurance, and other factors may be responsible, as suggested by SEARCH. [36] This is an area for further research since youth and young adults with diabetes face a longer lifetime exposure to hyperglycemia, hypertension, and obesity, which will likely result in increased risks of end-organ damage at an earlier age than among prior generations of patients with diabetes.

Summary and conclusions

SEARCH has provided substantial data on the current state of youth-onset diabetes in multiple race/ethnic groups:[128] American Indians [129], Asian Pacific Islanders [130], Hispanics [131], non-Hispanic Blacks [132], and non-Hispanic Whites [133]. These studies have included descriptive epidemiology of prevalence and incidence [7, 8], projections of future impact [15], metabolic investigations, such as the longitudinal changes in β cell function over time [134, 135], the role of glycemic control [136, 137], metabolic and genetic characteristics [22], types of treatment regimens and population differences in utilization [138], studies of out of pocket expenses [32], transition from pediatric to adult care [36], development of early microvascular complications by type within race/ethnic groups [3], and mortality compared with the U.S. age-appropriate population [30].

SEARCH has identified significant trends in youth onset diabetes. Both T1D and T2D are becoming more common in the U.S. youth[5]. Cardiovascular and microvascular risk factors are common and subclinical complications occur early, especially among youth with T2D and those of non-White race/ethnic backgrounds, [3] indicating a need for active intervention for detection and treatment of early complications at an earlier duration of diabetes than might have been expected. Multiple barriers to care have been identified, especially among persons of color and those with lower education, health insurance, and income. In adults, studies have shown improvements in diagnosis and care when insurance has become available [139–142], but even in managed care organizations, ethnic/racial differences remain

[143, 144]. Thus, future research may identify additional factors, perhaps partially embedded in systemic racism, that are operating. What is urgently needed is the identification of interventions that are efficacious, multifaceted, scalable, and affordable to begin to reduce these disparities.

SEARCH has shown that as youth with diabetes age, they transition from pediatric to adult care (or no care) at rates that differ by type of diabetes, insurance status, race/ethnicity, income, and other factors. Such transitions are points in the clinical course of illness that often result in poorer quality of care and poorer glycemic status [36], among other outcomes. Ways to improve transitions of care are needed.

SEARCH has provided population-wide estimates of burden and prognosis of youth-onset diabetes in the United States, very much like more established chronic disease registries, such as cancer. It is crucial to continue to invest in youth-onset diabetes surveillance and longitudinal studies focused on contemporary cohorts since these populations will bear the consequences of chronic diseases for much of their life.

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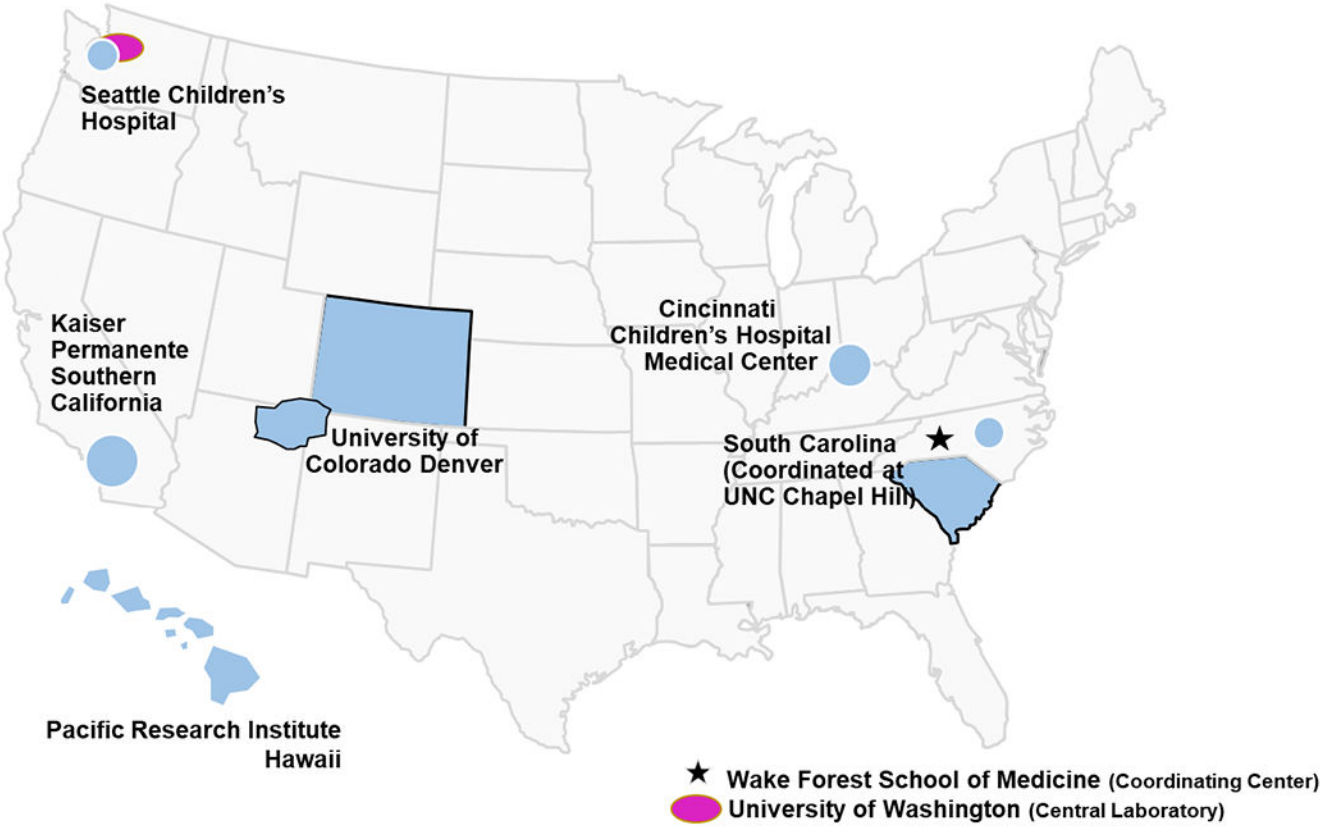


Figure 1.

Locations of SEARCH sites in the United States. Colorado and South Carolina included all counties in the states. Seattle and Cincinnati included defined counties surrounding the cities. The Southern California Kaiser Permanente included members except from San Diego and Colorado coordinated Native American sites in Arizona and New Mexico. Hawaii was included through phase 3 of SEARCH.

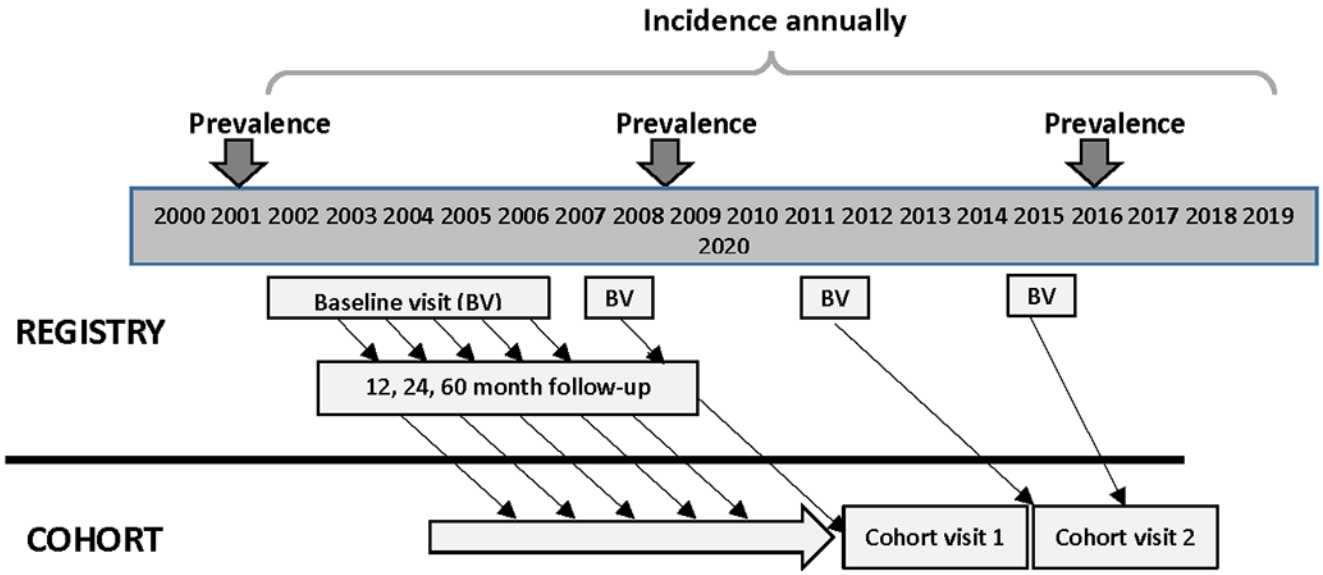


Figure 2.

The SEARCH study design summary. Prevalence was measured in the registry starting in 2001 and was repeated in 2009 and 2017. Incidence (new clinical diagnosis) was measured annually starting in 2002. Youth diagnosed in 2002–2006, 2008, 2012, and 2016 had a baseline in-person visit for measurement of diabetes autoantibodies, albuminuria, BMI, cardiovascular risk factors, and sociodemographic, quality of care, and quality of life questionnaires. Youth with baseline visits (incident cases in 2002–2005) were invited to return in 12, 24, and 60 months after their baseline visit for additional visits. Those with a baseline visit and at least 5 years of duration were asked to join the cohort study, from 2012 to 2020, which added measures of early complications (retinopathy, cardiac autonomic, and peripheral neuropathy, and arterial stiffness) in two visits.

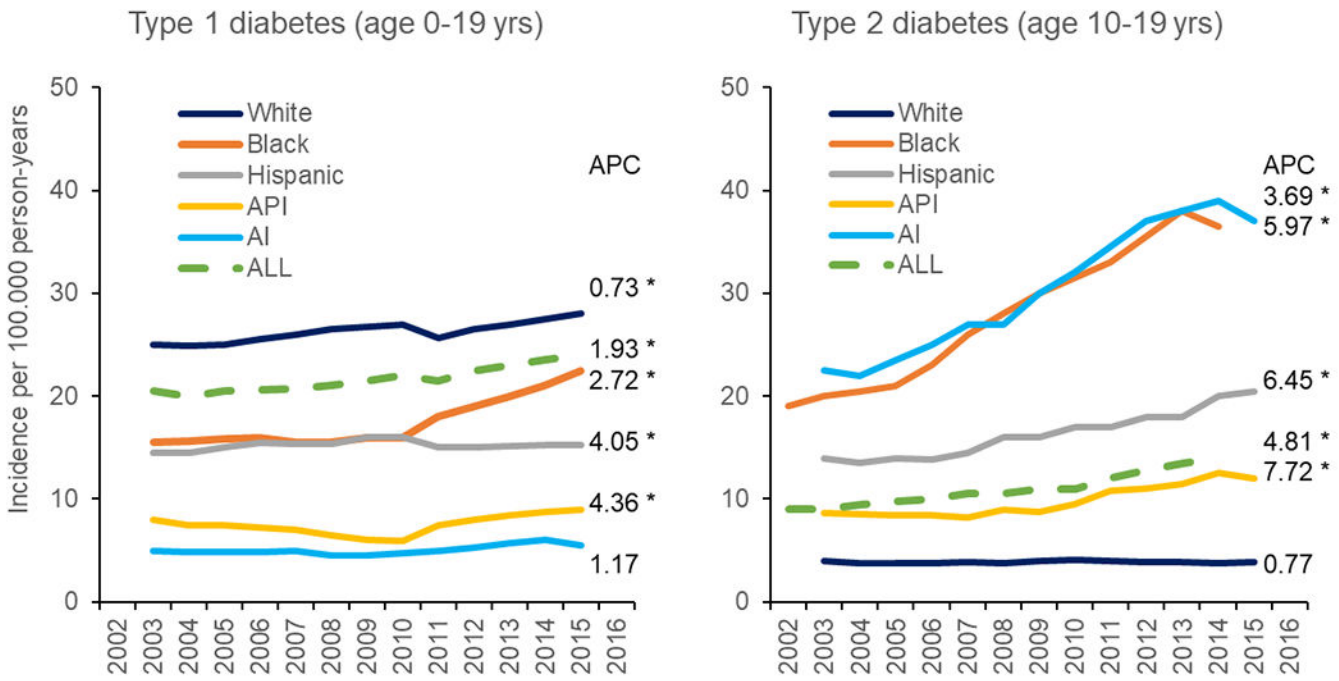


Figure 3.

Model-adjusted incidence rates of youth-onset T1D and T2D per 100,000 person-years overall and by race/ethnicity. SEARCH for Diabetes in Youth; 2002–2015. Persons who were AI were predominantly from one southwest tribe. Rates are 2-year moving averages. Overall model adjusted for age, sex, and race/ethnicity; race/ethnicity changes adjusted for age and sex. * $P < 0.05$. Modified from Ref. 5. AI, American Indian; APC, annual percent change in incidence based on a change model from 2020 – 2015; API, Asian Pacific Islander.

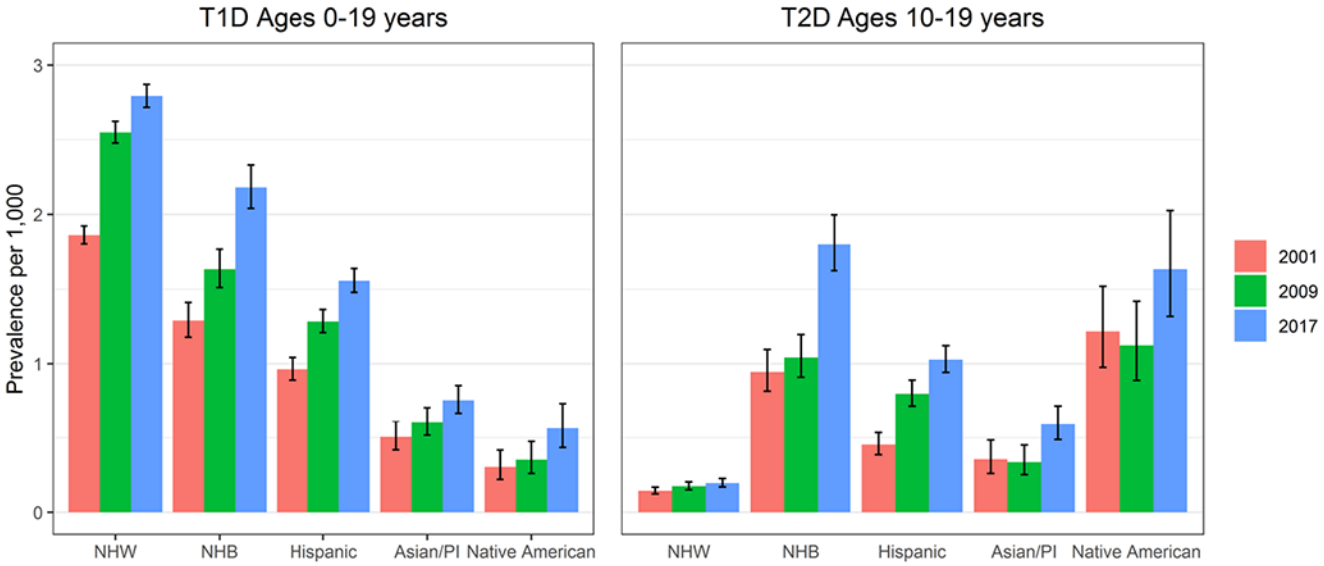


Figure 4.

Prevalence per 1000 Youth <20 years of age at onset by type (T1D and T2D) by Race/Ethnicity and year (2001, 2009, and 2017).[14] Significant increases ($P < 0.05$) in T1D and T2D were observed from 2001 to 2017 for each race/ethnicity group except for T2D among Native Americans ($P = 0.06$). The greatest increases in T1D were among NHW and NHB and for T2D, among NHB, Hispanics, and Asian/PIs. Asian/PI, Asian Pacific Islander; NHB, non-Hispanic Black; NHW, non-Hispanic White.

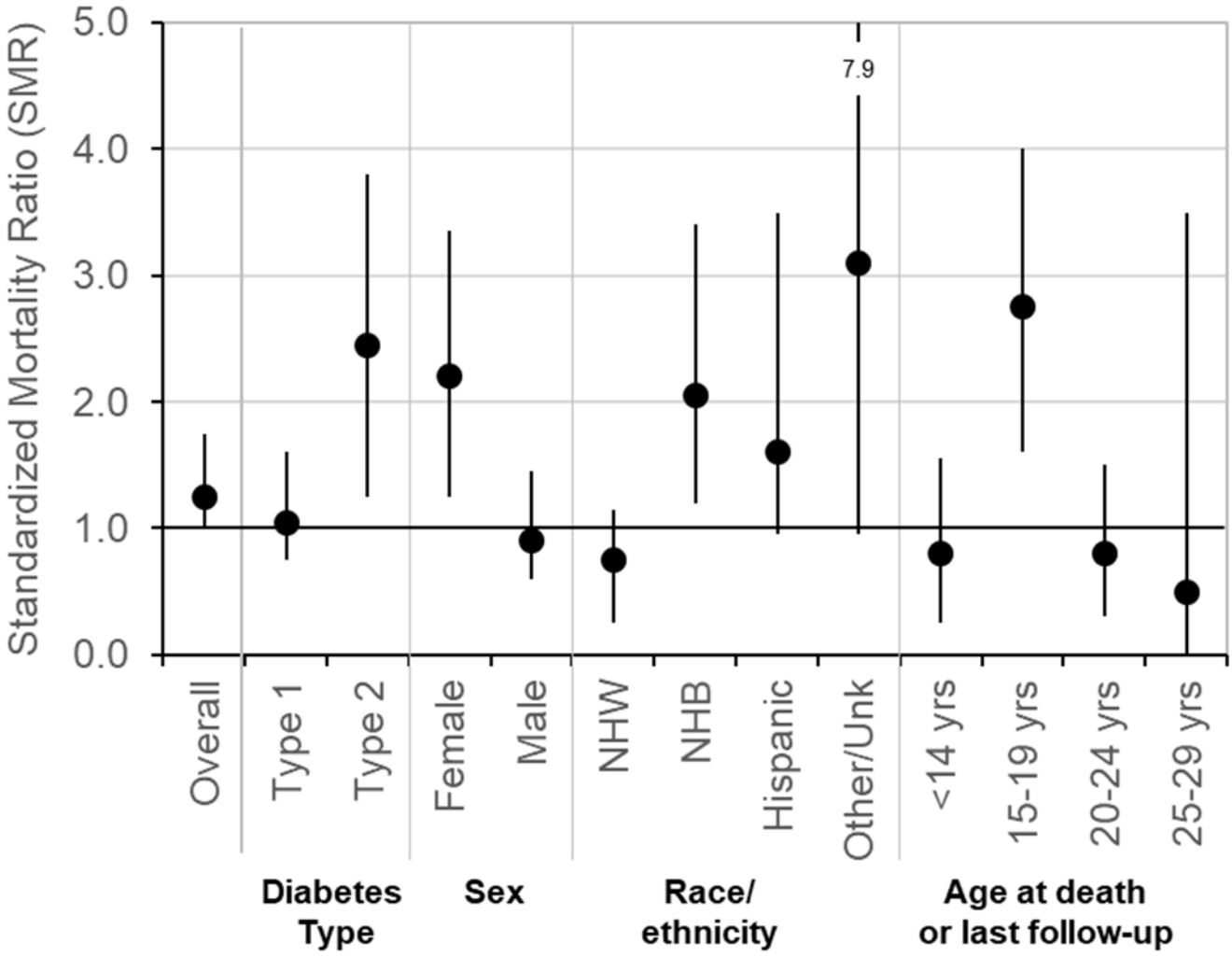


Figure 5.

Age-, sex-, and race-standardized mortality ratios for 6840 youth with T1D and 1518 youth with T2D stratified by diabetes type, sex, race/ethnicity and age in the SEARCH For Diabetes in Youth Study. Mortality rates in populations in the same geographic areas were used as referents. NHB, non-Hispanic Black; NHW, non-Hispanic White. Modified from Ref. 30.

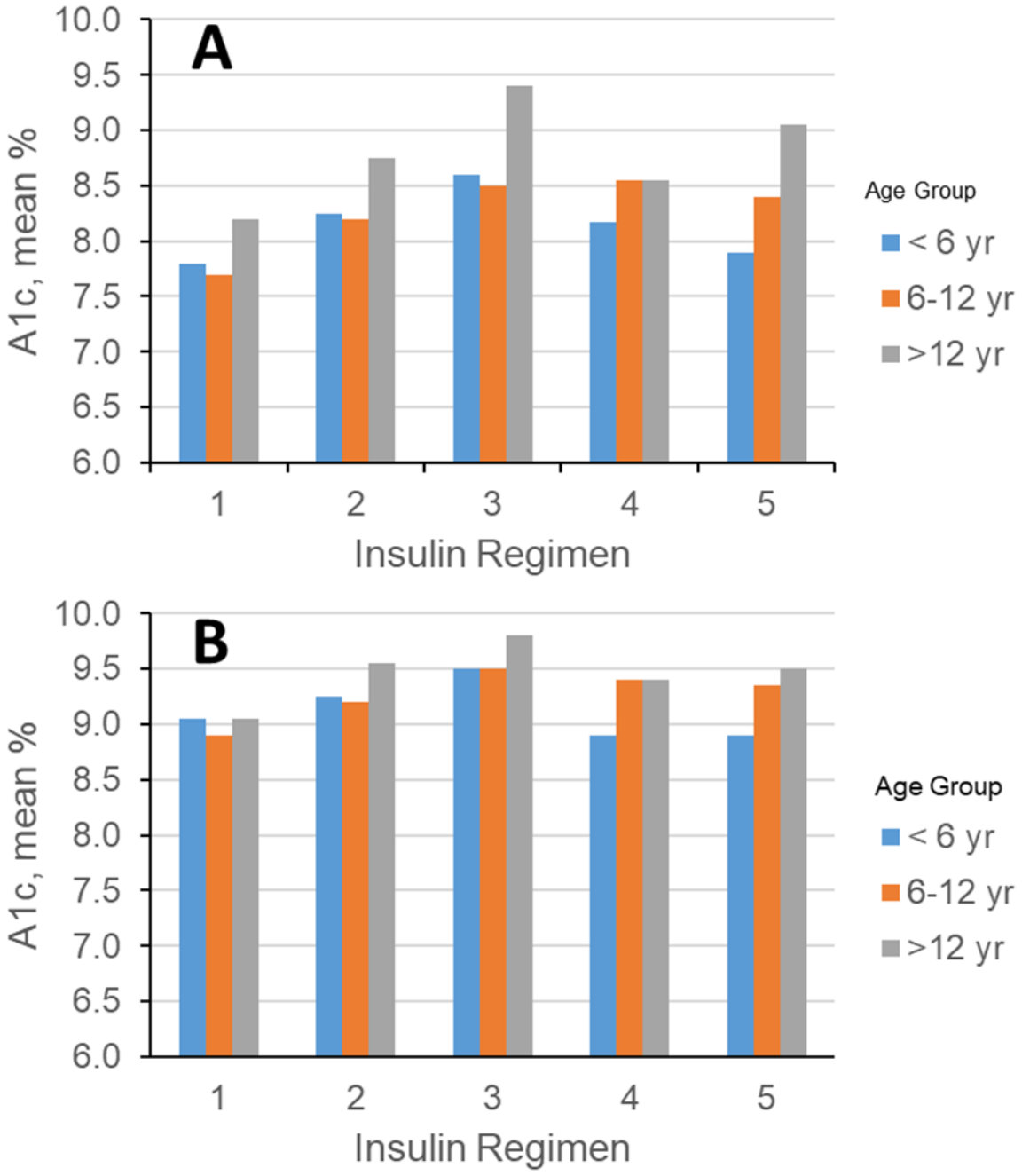
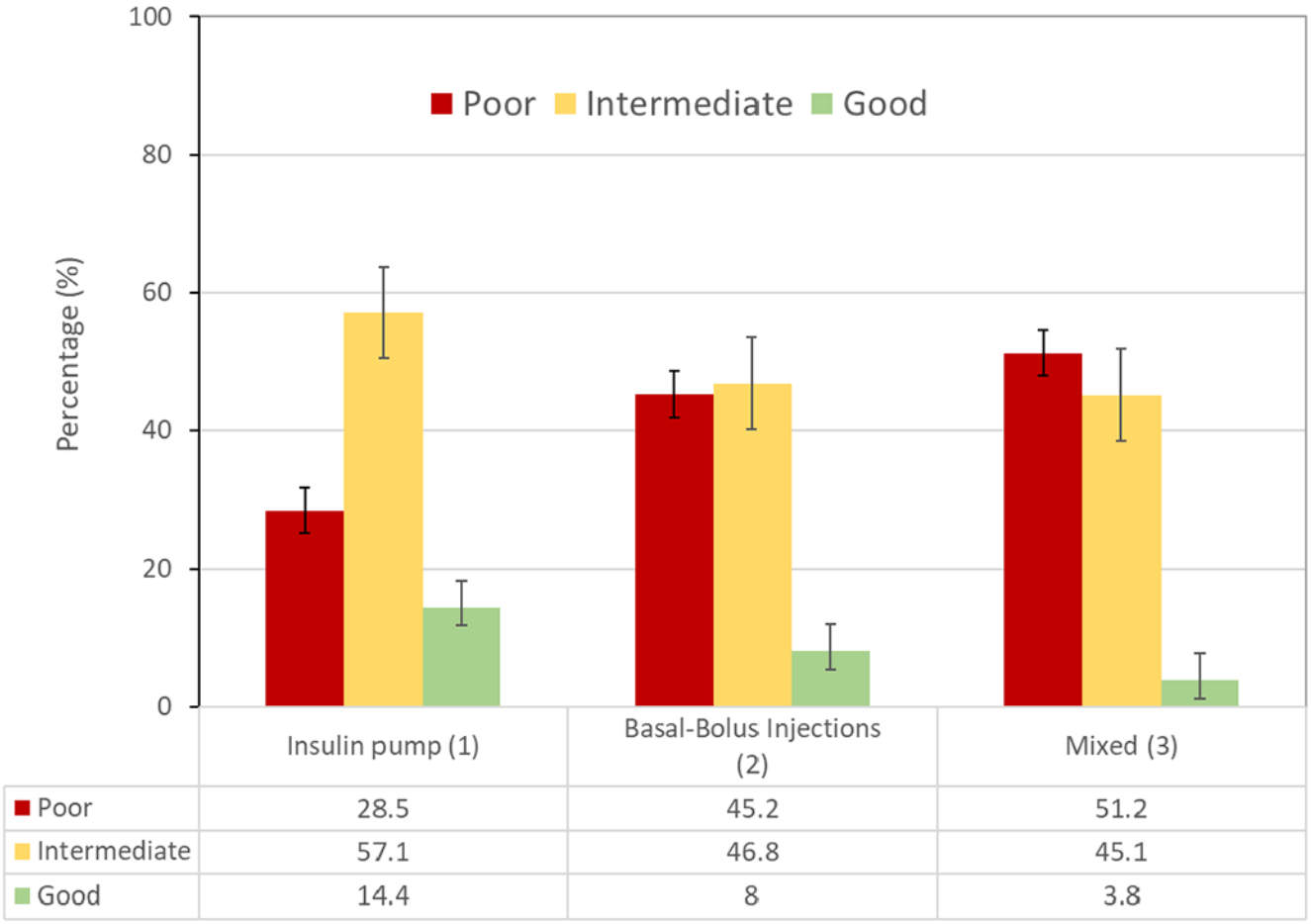


Figure 6.

Mean A1C (%) by age group and insulin regimen. (A) Unadjusted and (B) adjusted for sex, race/ethnicity, income, education, insurance, center, DM duration, and frequency of glucose monitoring. Insulin regimens: (10) insulin pump; (2) glargine + rapid-acting insulin; (3) glargine + two or more insulins; (4) multiple injections w/o glargine; and (5) two or fewer insulin injections. Modified from Ref. 33.



	Insulin pump (1)	Basal-Bolus Injections (2)	Mixed (3)
Poor	28.5	45.2	51.2
Intermediate	57.1	46.8	45.1
Good	14.4	8	3.8

Figure 7.

Glycemic control (percent with 95% confidence intervals) within insulin regimen groups for youth onset T1D in the SEARCH for Diabetes Study. Poor A1c ≥9.5%; intermediate A1c 7.5% to ˂9.5%; and good A1c ˂7.5%. Insulin regimens were classified into three categories: (1) basal–bolus with continuous subcutaneous infusion (insulin pump therapy); (2) basal–bolus injections with glargine or detemir plus rapid-acting insulin (insulin lispro, insulin aspart, or insulin glulisine); and (3) mixed insulin regimen consisting of (a) multiple daily injections (≥3 injections) with glargine or detemir insulin plus NPH insulin plus regular or rapid-acting insulin, (b) multiple daily injections (≥3 injections) with any insulin types excluding basal insulin (glargine or detemir), or (c) one to two injections per day, excluding insulin glargine or detemir. Modified from Ref. 34.

Table 1.

Age-adjusted prevalence of early diabetes–related chronic complications and comorbidities by diabetes type among 2018 youth and young adults with the duration of 8 years, SEARCH for Diabetes in Youth Study

Complication and race/ethnicity category	Type 1 diabetes *N* = 1746	Type 2 diabetes *N* = 272	Risk difference (Type 2 - Type 1)	*P*
	% (95% CI)	% (95% CI)	% (95% CI)	
Diabetic kidney disease	**5.8 (4.6 to 7.4)**	**19.9 (15.1 to 25.7)**	**14.0 (9.1 to 19.9)**	**<0.001**
Retinopathy	**5.6 (4.4 to 7.0)**	**9.1 (6.3 to 12.9)**	**3.5 (0.4 to 7.7)**	**0.02**
Peripheral neuropathy	**8.5 (7.1 to 10.2)**	**17.7 (13.6 to 22.7)**	**9.2 (4.8 to 14.4)**	**<0.001**
Cardiovascular autonomic neuropathy	14.4 (12.5 to 16.6)	15.7 (11.7 to 20.6)	1.2 (−3.1 to 6.5)	0.6
Arterial stiffness	**11.6 (9.8 to 13.6)**	**47.4 (40.3 to 54.7)**	**35.9 (29 to 42.9)**	**<0.001**
Hypertension	**10.1 (8.6 to 11.9)**	**21.6 (17.1 to 26.9)**	**11.5 (6.8 to 16.9)**	**<0.001**

Rows in BOLD are statistically significant at $P < 0.05$

Prevalence is model derived and adjusted to a duration of 8 years and an age of 21 years.

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Table 2.

Statistically significant behavioral, psychological, and social associations of pediatric onset T1D and T2D, the SEARCH for Diabetes in Youth Study

	Age at onset and progression		Glycemic control		Cardiovascular risk factors	
	T1D	T2D	T1D	T2D	T1D	T2D
Behavioral						
↓ Sugar-sweetened beverages	↑ Age at onset		↓ A1c		↓ Dyslipidemia	
↓ Juice	↑ Age at onset					
↓ Diet beverages			↓ A1c		↓ Dyslipidemia	
↓ Eggs, potatoes, and high-fat meat			↓ A1c		↓ Obesity, dyslipidemia, blood pressure, and arterial stiffness	
↑ DASH diet			↓ A1c		↓ blood pressure	↓ Obesity, dyslipidemia, and blood pressure
↑ Protein			↓ A1c			
↓ Carbohydrates			↓ A1c			
↓ Fructose					↓ Blood pressure	
↑ Fatty acid	↑ c-peptide		↓ A1c			
↑ Leucine	↑ c-peptide		↓ A1c			
↑ Vitamin D	↓ Insulin resistance				↓ Obesity	
↓ Trans-fatty acids					↓ Blood pressure and dyslipidemia	
↑ Counting carbohydrates			↓ A1c	↓ A1c	↓ Dyslipidemia	
↓ Daily eating episodes			↓ A1c	↓ A1c		
↓ Screen time			↓ A1c	↓ A1c	↓ Dyslipidemia	
↓ Smoking					↓ Dyslipidemia	
Psychological						
↓ Depressive symptoms			↓ A1c	↓ A1c		
↓ Diabetes-related quality of life			↓ A1c	↓ A1c		
↓ Unhealthy weight loss practices			↓ A1c	↓ A1c		
↓ Disordered eating behaviors			↓ A1c	↓ A1c		

	Age at onset and progression		Glycemic control		Cardiovascular risk factors	
	T1D	T2D	T1D	T2D	T1D	T2D
Social						
Medium population density	↑ Incidence					
↓ Neighborhood affluence	↓ Incidence					
↓ Rurality		↓ Incidence				
↑ Supermarket density					↓ Obesity	↓ Obesity
↑ Proximity to fast-food outlets					↓ Obesity	↓ Obesity
↓ Food insecurity			↓ A1c			

Note: All results are from SEARCH papers referenced in this article.
BP, blood pressure; T1D, T1D diabetes; T2D, T2D diabetes.