



Diabetes in Youth—Looking Backwards to Inform the Future: Kelly West Award Lecture 2017

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The Kelly West Award for Outstanding Achievement in Epidemiology is presented in honor of the memory of Kelly M. West, widely regarded as the “father of diabetes epidemiology.” Harry Keen described West as characterized by “generosity of spirit, deeply human and humorous, deliberate of address, modest, conciliatory and untiringly persevering. Few people have done so much to change the landscape of diabetes” (1). The award and lecture recognize a leading epidemiologist in the field of diabetes. Dana Dabelea, MD, PhD, received this award at the American Diabetes Association’s 77th Scientific Sessions, 9–13 June 2017, in San Diego, CA. She presented the Kelly West Award Lecture, “Diabetes in Youth—Looking Backwards to Inform the Future,” on Sunday, 11 June 2017.

The face of pediatric diabetes has undergone striking changes over several decades. Epidemiology has shown that type 1 diabetes incidence has been increasing worldwide, with wide geographic variation in absolute risk (2). Similarly, more recently, type 2 diabetes has been increasing primarily in indigenous youth as never before (2). In addition, the obesity epidemic has changed the phenotype of type 1 diabetes, prompting suggestions that some youth have “type 1.5 diabetes,” or even “double diabetes.” Can we identify factors responsible for these changes? We propose that “looking backwards” in time and at early stages in the life course of individuals will provide new and useful clues to the etiology and prevention of diabetes.

This review focuses on three related themes, and each one has been augmented by “looking backwards”: 1) surveillance of diabetes in youth, 2) the developmental origins of pediatric obesity and diabetes, and 3) diabetes prevention throughout the life course. Examples of data on diabetes burden in youth, complications, prevalence, and projections are provided. Also discussed is the Developmental Origins of Health and Disease (DOHaD) paradigm, which posits that various exposures during critical periods, such as pregnancy or early life, predispose the fetus and newborn to health or disease later in life. The integration of basic science in these life-course studies provides a unique window into potential biologic mechanisms. The notion of a “vicious cycle of diabetes and obesity” is described, and studies attempting to break the cycle are reviewed. A comprehensive approach to prevention throughout the life course is proposed, given data that poor lifestyle habits exist throughout childhood into adulthood. While diabetes can be prevented or delayed in adults, a much earlier primordial prevention approach is needed that begins before birth and extends through childhood.

HISTORICAL PERSPECTIVE: “LOOKING BACKWARDS”

Looking backwards in time, at the start of the 20th century, type 1 diabetes was a rare and rapidly fatal disease. Youth were thin and usually of white race/ethnicity. The incidence in 1900 in Norway was 2 per 100,000 per year rising to 7 per 100,000 per year by 1920 (3). In 1923, 86% of youth with type 1 diabetes died of diabetic ketoacidosis. However, after

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the discovery of insulin, the incidence of type 1 diabetes began to increase. Over the past 40 years of the previous century, increases of 2–4% per year, largely across Europe, were reported by multiple studies (4,5). In parallel, there was a decrease in the age of onset of type 1 diabetes (3).

Type 2 diabetes, not considered a pediatric disease until recently, was often called adult-onset diabetes. Over the past decade of the 20th century, there were a number of reports of obesity-associated type 2 diabetes in youth, especially minority youth, in clinic-based studies (6–8) (Fig. 1A). In one of the earliest population-based reports, we showed that prevalence had increased over three decades by approximately 80% in Pima Indians (9) (Fig. 1B). It was becoming clear that the face of pediatric diabetes was changing. However, at the start of 21st century, there were limited U.S. data on the epidemiology of pediatric diabetes, regardless of type.

BURDEN OF TYPE 1 AND TYPE 2 DIABETES IN CONTEMPORARY U.S. YOUTH

This motivated the Centers for Disease Control and Prevention and the National

Institute of Diabetes and Digestive and Kidney Diseases to fund the SEARCH for Diabetes in Youth (SEARCH) study, covering all elements of a surveillance system, monitoring trends, developing projections of burden, understanding contemporary clinical management, and evaluating the risk of complications. SEARCH has been accomplishing all these goals for over 15 years (10).

One of the first SEARCH contributions was providing baseline incidence data of type 1 and type 2 diabetes in U.S. youth by age and race/ethnicity for year 2002–2003 (Fig. 2) (11). Data showed a striking race/ethnicity pattern that goes in opposite directions for type 1 versus type 2 diabetes, with highest rates of type 1 diabetes in non-Hispanic whites (NHW), followed by non-Hispanic blacks (NHB), Hispanics (HISP), and Asian Pacific Islanders (API), with little type 1 diabetes in American Indians/Alaskan Natives (AIAN). In contrast, the highest rates of type 2 diabetes are in minority children, AIAN, NHB, HISP, and API, with the lowest rates in NHW youth. Absolute rates of type 2 diabetes tended to be higher than rates of type 1 diabetes among most minority groups.

SEARCH recently published the first comprehensive assessment of trends in the incidence rates of type 1 and type 2 diabetes in U.S. youth between 2002 and 2012 (12) (Fig. 3). Age-, sex-, and race/ethnicity-adjusted type 1 diabetes rates (Fig. 3A) increased on average by 1.8% per year ($P = 0.03$). In pairwise comparisons, the annual rate of increase was greater among HISP than among NHW (4.2% vs. 1.2%, $P < 0.001$). There was no significant increase among AIAN youth. In contrast, type 2 diabetes rates (Fig. 3B) increased by 4.8% per year on average ($P < 0.001$), with the largest increases in AIAN (8.9% per year) and NHB youth (6.3% per year), with no significant increase in NHW.

These data allowed us to update the worldwide picture of type 1 diabetes in youth with contemporary SEARCH information (Fig. 4). The SEARCH incidence data are in the middle, following closely past trends in predominantly white populations from Allegheny County, PA, and Colorado, with northern European and Scandinavian countries having higher rates over time (2). Predominantly non-white countries, like China and Japan, although showing increasing rates over time, have the lowest risk of type 1

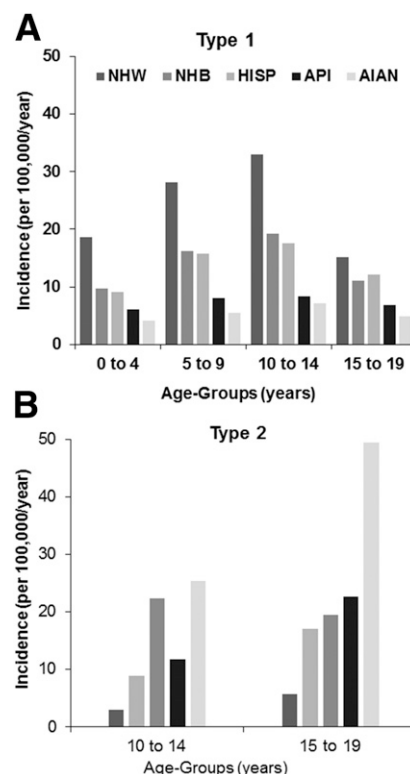


Figure 2—A: Incidence rates (per 100,000 per year) for type 1 diabetes with onset <20 years of age in 2002–2003 in SEARCH. Based on 1,905 youth with type 1 diabetes in 10 million person-years at risk. B: Incidence rates (per 100,000 per year) for type 2 diabetes with onset <20 years of age in 2002–2003 in SEARCH (11). Based on 530 youth with type 2 diabetes in 10 million person-years at risk. For children aged 0 to 4 years and 5 to 9 years, virtually all diabetes was type 1, regardless of race/ethnicity, so data are not shown.

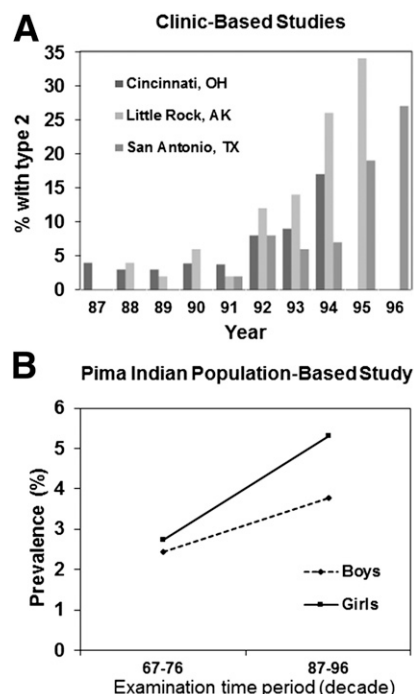


Figure 1—The changing face of diabetes in youth. A: Increasing proportion of youth in diabetes clinics with type 2 diabetes between 1987 and 1996 (6–8). B: Increasing prevalence of type 2 diabetes among Pima Indian girls and boys between two studies conducted between 1967 and 1976 and 1987 and 1996 (9).

diabetes. What does this worldwide picture mean? Genetic differences in populations likely underlie the broad spread in absolute incidence rates, for example, between Finland and China. However, the increases have occurred over a short time period, making genetic changes in the populations unlikely. Such changes strongly suggest the role of environmental factors in the etiology, and many have been suggested, including exposures during pregnancy, type of birth delivery, infant diet, gut microbiota, and viruses.

We do know that these increases have occurred in parallel with a decrease in the frequency of high-risk HLA genotypes and an increase in the frequency of moderate/low-risk genotypes in NHW and HISP youth with type 1 diabetes (13). This suggests that, over time, the environmental triggers of type 1 diabetes (as yet largely

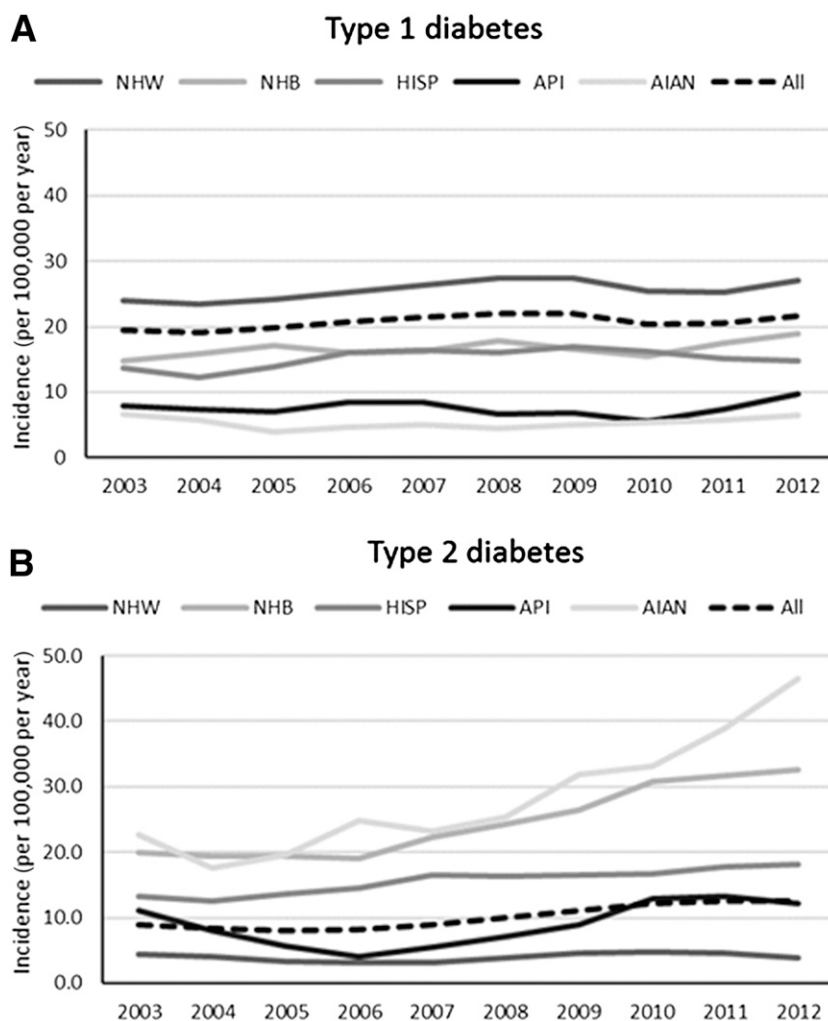


Figure 3—A: Age-, sex-, and race/ethnicity-adjusted type 1 diabetes incidence rates (per 100,000 per year) by race/ethnicity and year of diagnosis (12). Over all race/ethnicity groups, type 1 diabetes rates increased 1.8% per year (dashed line). **B:** Age-, sex-, and race/ethnicity-adjusted type 2 diabetes incidence rates (per 100,000 per year) by race/ethnicity and year of diagnosis. Over all race/ethnicity groups, type 2 diabetes rates increased 4.8% per year (dashed line). Adapted with permission from Mayer-Davis et al. (12).

unknown) have become more widespread, partially alleviating the need for a strong genetic background as the primary risk factor.

SEARCH data allowed us to explore trends in type 2 diabetes rates in the context of North American youth (Fig. 5). SEARCH rates are shown in solid lines and follow closely prior trends by race/ethnicity reported from Chicago (14) and in First Nation youth from Canada (dotted lines) (15). This indicates that the increasing risk of type 2 diabetes in youth has been happening for several decades. Data from the National Health and Nutrition Examination Survey (NHANES) (16) have shown that the rise in type 2 diabetes follows four decades of greater overweight and obesity among

U.S. youth, pointing to this environmental contribution. Factors such as the increase in maternal diabetes during pregnancy (17), a strong risk factor for type 2 diabetes in offspring (9), also have to be considered.

Youth under surveillance by SEARCH closely approximate the distribution of the U.S. Census data for youth aged <20 years in terms of race/ethnicity, age-group, education, and median household income (18). This allowed estimation of the number of youth with diabetes in 2009, using U.S. Census data. Approximately 191,986 youth were identified with physician-diagnosed diabetes, 166,984 with type 1 diabetes, 20,262 with type 2 diabetes, and 4,740 with a mixture of “other” types. There were 18,400 youth diagnosed with type 1 diabetes annually

(incident cases), and 5,100 youth diagnosed with type 2 diabetes (19).

PROJECTIONS OF FUTURE BURDEN

SEARCH data have allowed diabetes projections into the future. Markov modeling was used to estimate the numbers of youth with diabetes in the year 2050 using two possible scenarios, one of constant future incidence and one of annually increasing incidence (20). Under the second scenario (more likely given the evidence of rising rates reported by SEARCH), the projected prevalence is likely to increase from observed levels in 2010 by almost threefold for type 1 diabetes and fourfold for type 2 diabetes by 2050, with a substantially higher burden among minority youth for both types (20).

COMPLICATIONS PATTERNS

The burden of diabetes in youth is important; however, it is perhaps even more important to determine its consequences. Figure 6 identifies a troublesome constellation of complications and comorbidities among youth with both types of diabetes. For each complication, with the exception of cardiac autonomic neuropathy, the prevalence is significantly higher in type 2 versus type 1 diabetes, especially among minority youth, but the prevalence is high in both types.

At an average age of 21 years and a duration of disease of a little less than 8 years, one in three youth with type 1 diabetes and three in four youth with type 2 diabetes had at least one such complication or comorbidity (21).

The data summarized above have shown 1) increasing incidence of both type 1 and type 2 diabetes, especially among minorities; 2) changes in the environment in which children are born and grow are likely causes; and 3) there is a high burden of early diabetes complications, which are higher in youth with type 2 diabetes and in minority youth. These patterns suggest that higher costs and greater societal burden are very likely in the next 20–30 years. Clearly, we need to understand the causes of these changes to understand how to develop effective prevention approaches. As these changes are occurring in youth and young adults, taking a developmental origins approach is warranted.

DOHaD

Our approach is based on the DOHaD paradigm, which posits that various exposures

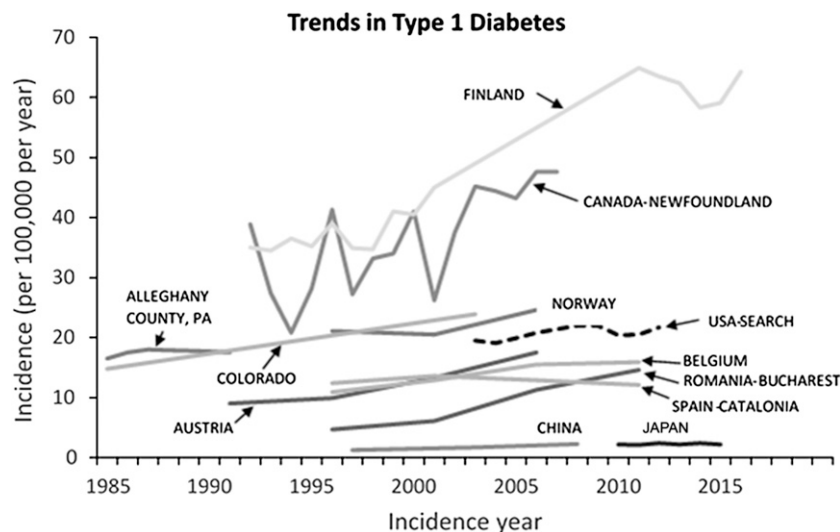


Figure 4—Temporal trends in type 1 diabetes by geographic location and incidence year (2). The dashed line is contemporary U.S. data from SEARCH (12).

(nutritional, chemical, physical, social, environmental, etc.) during critical periods, such as during pregnancy or early life, predispose the developing organism to health or disease later in life. Such critical periods continue to exist during postnatal life—early life, adolescence, puberty, and again pregnancy—thus potentially creating and perpetuating a transgenerational cycle of health and disease at the population level.

DIABETES IN PREGNANCY

There is a substantial body of evidence in support of this paradigm from studies of diabetes in pregnancy. Among the Pima

Indians, offspring of women with diabetes during pregnancy had a higher prevalence of type 2 diabetes and were more obese than those who were not exposed to diabetes during pregnancy (22). Over 70% of people with prenatal exposure had type 2 diabetes by 25–34 years of age. Fetal exposure to maternal diabetes in utero was the strongest single risk factor for type 2 diabetes in Pima youth, with an odds ratio (OR) of 10.4. Findings from the Pima Indian study provided strong evidence that using this approach would lead to important findings when applied to both obesity and diabetes. We found a similarly strong association in a racial and

ethnically diverse group of youth and control subjects in the SEARCH Case-Control (SEARCH-CC) study, an OR of 7.3 (23).

Not only were these strong associations but they also reflected specific intrauterine effects. This was elegantly demonstrated among the Pima Indians using a sib-pair design with siblings born before and after their mothers were diagnosed with diabetes (24). Among 28 sib-pairs discordant for exposure to diabetes in utero, 21 of 28 developed diabetes after their mother was diagnosed with diabetes during pregnancy and only 7 developed diabetes before the mother was diagnosed. The OR of 3.7 ($P = 0.02$) for the association between type 2 diabetes in youth and exposure to maternal diabetes in utero among sib-pairs virtually controls for the genetic predisposition to diabetes transmitted from mother to offspring. It also controls for postnatal shared familial risk factors and thus isolates the specific intrauterine effects, yet unknown, that are responsible for this association. The fact that this association was not present in sib-pairs born before or after the father was diagnosed with diabetes also reduces the concern for a chance finding or birth order effects.

Ultimately, this strong association is important because of its public health impact. Among the Pima Indians, exposure of the fetus to maternal diabetes during pregnancy was responsible for 35% of type 2 diabetes in 5- to 19-year-old children between 1987 and 1996, approximately twice the attributable risk found between 1967 and 1976. In a more diverse population enrolled in SEARCH-CC, we found that 47.2% of type 2 diabetes with onset at ≤ 20 years old could be attributed to maternal diabetes, obesity, and their combination (23). This also means that it could be prevented were we successful in eliminating exposure to diabetes and obesity during pregnancy.

BEYOND DIABETES IN PREGNANCY

However, it is not just diabetes in pregnancy that needs to be controlled but also obesity and other exposures during pregnancy and postnatal life that may contribute to long-term risk. Therefore, we have moved beyond pregnancy diabetes toward a more comprehensive assessment of early-life exposures.

An example of such work is the Healthy Start Study (Exploring the Fuel-Mediated Programming of Neonatal Growth) study

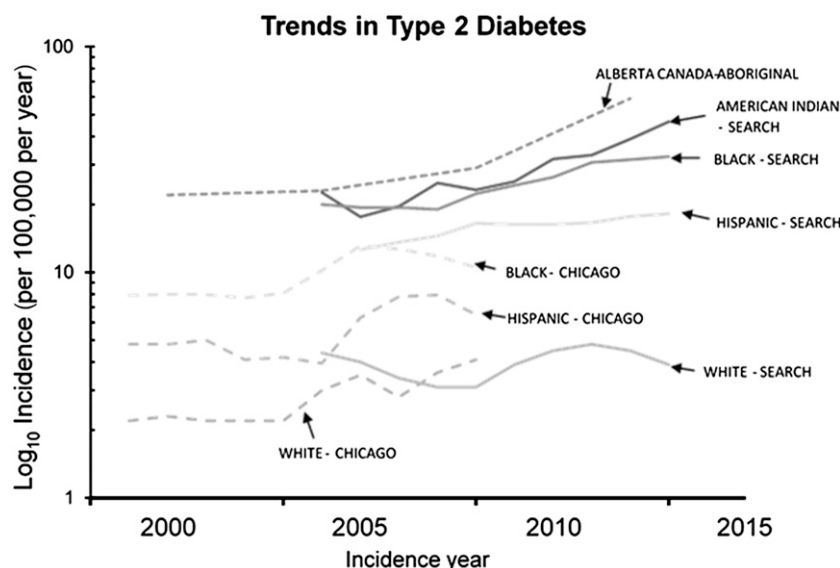


Figure 5—Temporal trends in incidence rates for type 2 diabetes by geographic area and year of diagnosis. SEARCH data are shown in solid lines (2).

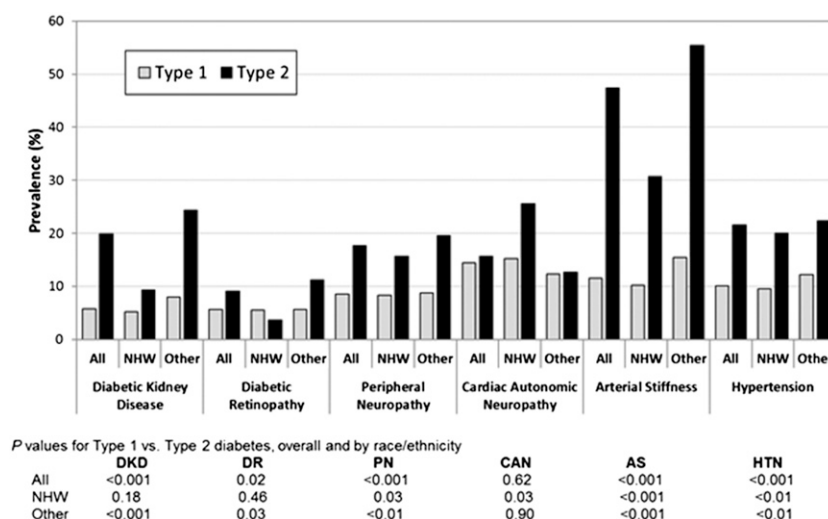


Figure 6—Prevalence of diabetes complications and comorbidities by type of outcome and race/ethnicity, adjusted to 21 years of age (21). Other, NHB, HISP, API, and AIAN combined.

in Colorado, a prebirth cohort of 1,410 mother-offspring dyads followed from early pregnancy through delivery and into childhood. We are examining multiple nutritional, chemical, physical, and social exposures during pregnancy and early life and exploring their biologic signatures (through “omics” research) to develop the early-life “exposome” and link it to childhood outcomes, including growth, adiposity, cardiometabolism, neurocognition, and behavior. The study is part of the large Environmental Influences on Childhood Health Outcomes (ECHO) consortium, a National Institutes of Health effort to develop a cohort of over 50,000 youth to understand the environmental triggers of many chronic childhood diseases.

The Healthy Start Study has already produced findings about the role of in utero exposures with mechanistic insights and clinical relevance. For example, independent of prepregnancy BMI, increased gestational weight gain in all three trimesters was associated with increased neonatal adiposity, measured by air displacement plethysmography (an increase in the percentage of neonatal fat mass of 0.55 units for each 0.1 kg of gestational weight gain per week, $P < 0.001$) (25). Maternal high- versus low-fat diet was associated with 0.8 units higher neonatal fat mass percent, independent of prepregnancy BMI, energy intake, and expenditure (26). Increasing levels of late-pregnancy physical activity were associated with decreased neonatal adiposity (41.1 g less neonatal fat mass, $P = 0.03$)

without significantly reduced lean mass (27). Maternal glucose levels, even within the normal range, were found to mediate 20% of the association between maternal BMI and neonatal adiposity, whereas other fuels that cross the placenta, such as triglycerides and free fatty acids, were not related (28,29).

Healthy Start Study investigators also collaborate with basic scientists through the BabyBump project (Baby Biology of Intra-Uterine Metabolic Programming), the mechanistic arm of the Healthy Start Study. We have isolated, grown, and stored mesenchymal stem cells from umbilical cord tissue samples collected at birth. These cells differentiate into numerous cell lines, adipocytes, myocytes, astrocytes, etc., and various teams are conducting in vitro and in vivo studies to elucidate the mechanisms responsible for programming of obesity. We have found greater adipogenesis in mesenchymal stem cells from obese versus normal-weight mothers mediated by the β -catenin system, providing a potential pathway through which maternal overweight programs stem cells toward adiposity (30).

Similarly, collaboration with genomic experts is identifying epigenetic signatures of in utero exposures, such as gestational diabetes mellitus (GDM). In another cohort study in Colorado (Exploring Perinatal Outcomes among Children [EPOCH] Study), we conducted an epigenome-wide association study among 10-year-old youth who were exposed and not exposed to GDM and identified

98 differentially methylated regions. Given the strength of association, effect size, network analysis, replication in cord blood in a subsample, and prior literature, we prioritized nine genes for pyrosequencing. This validated six out of nine genes, of which some were also associated with obesity-related outcomes in 10-year-old children (31).

ROLE OF EARLY POSTNATAL NUTRITION

Although prenatal exposures are clearly important, postnatal ones, especially in the first 2 years of life (the first 1,000 days, roughly from conception to the second birthday), are also important. Data from the Pima Indian study have shown a strong protective effect of breastfeeding (vs. bottle-feeding) in the first 3 months of life against early-onset type 2 diabetes with an adjusted OR of 0.41 (32). In the EPOCH cohort, we showed that breastfeeding modified the effect of exposure to diabetes in utero on obesity outcomes in the offspring (33). Among those breastfed for less than 6 months, BMI was significantly higher in those exposed versus not exposed to diabetes in utero; however, in those breastfed for 6 or more months, the effect of exposure was attenuated to non-significance. Similar results were seen for waist circumference and visceral and subcutaneous adipose tissue, suggesting a potential postnatal intervention in high-risk infants.

Colleagues at the Barbara Davis Center for Childhood Diabetes in Colorado are also studying infant and early-life diet in relation to type 1 diabetes risk. Data from the Diabetes Autoimmunity Study in the Young (DAISY) suggest that timing of nutritional exposures is relevant for type 1 diabetes risk (34). Early (before 4 months) and late (after 6 months) introduction of any solid foods and early and late introduction to any cereals all increase the risk of type 1 diabetes from 1.7-fold to over 3-fold, while breastfeeding at introduction of cereals reduces risk by about 50%. Thus, postnatal nutrition is important for type 1 diabetes risk as well.

Given the evidence of the importance of good nutrition and active lifestyles, it is unfortunate that most U.S. youth do not meet the recommendations for eating 2.5–6.5 cups of fruits and vegetables each day, do not eat the minimum recommended amounts of whole grains (2–3 ounces each day), eat more than the

recommended maximum daily intake of sodium (1,500–2,300 mg each day), and have 40% of daily calories coming from “empty calories” (sugars and solid fats). In addition, only 29% percent of high school students had participated in at least 60 min per day of physical activity on each of the 7 days before the survey (35). This suggests that a successful approach to prevention of obesity and diabetes, as well as asthma, heart disease, and selected cancers, requires a comprehensive life-course approach.

A COMPREHENSIVE APPROACH TO PREVENTION THROUGHOUT THE LIFE COURSE

There is now definitive evidence from the Diabetes Prevention Program (DPP) study, which we are proudly part of, that metformin and especially lifestyle interventions reduced diabetes risk in adults by 31–58% (36). These effects were sustained over 15 years (37), with heart disease and stroke risk factors also reduced with fewer medications. In addition, we have now evidence, informed by surveillance systems, that the annual rate of diabetes development in U.S. adults, after a steady increase, may be decreasing for the first time in 20 years, by about 5.4% per year (38). There are now 1.4 million fewer new reported cases in the U.S. each year. We may have turned the corner, perhaps as a consequence of DPP and DPP-like (39) translational programs, though contrary opinions exist about these trends (40). Unfortunately, we are seeing an opposite trend of similar magnitude in pediatric diabetes. To us, this means that we need to increase or shift the focus on prevention earlier in life, working toward “primordial” prevention.

The notion of a “vicious cycle of diabetes and obesity” was first described by Pettitt and Knowler (41) (Fig. 7). Young women who are obese or have diabetes during pregnancy have a higher risk that their offspring will also be obese or develop diabetes later in life. As these youth enter young adulthood, obese women or women with diabetes transmit this increased risk to the next generation. It is likely that this vicious cycle must be broken earlier and at different levels during the life course if we are to make greater strides toward reduction of diabetes and obesity. There are multiple points along the circle where attempts have been made, as shown in Fig. 7. Some of these

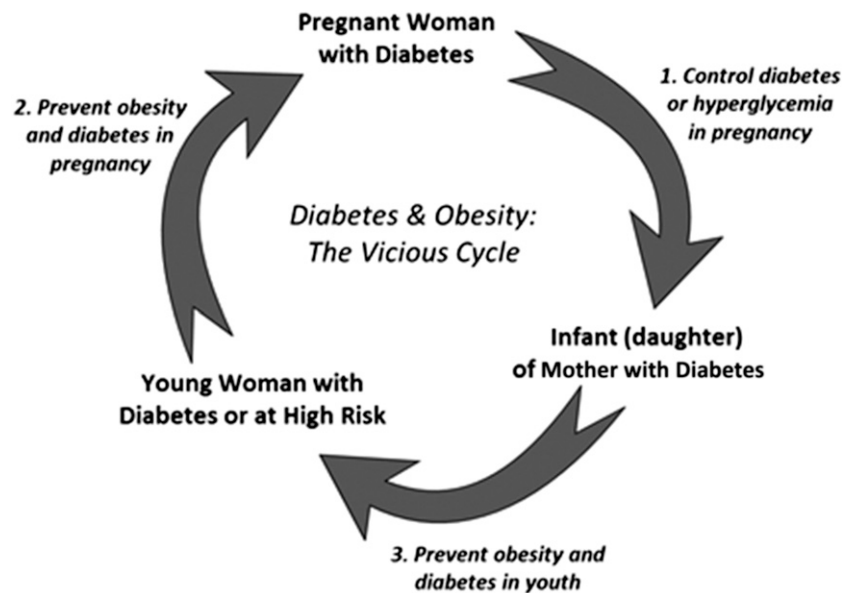


Figure 7—The vicious cycle of transgenerational obesity and diabetes, including potential times when the cycle might be broken through effective interventions.

include 1) controlling diabetes or hyperglycemia in pregnancy, 2) preventing obesity and diabetes in pregnancy, and 3) preventing obesity and diabetes in youth.

One strategy has been to control diabetes or hyperglycemia in pregnancy. A randomized trial of glucose control among women with mild GDM was conducted, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) (42). The intervention included dietary and lifestyle advice, and a usual-care group was blinded to the “diagnosis” of GDM, which was not treated unless symptomatic. ACHOIS confirmed that GDM has relatively rare but serious adverse perinatal effects and that treatment is beneficial in avoiding them. However, in an observational follow-up of offspring at ages 4 to 5 years born to mothers in ACHOIS, no effect was seen on offspring BMI z-scores between groups (43). Why these results were negative is uncertain. It may be because GDM was mild in all mothers in both arms of the trial or that excess obesity among offspring may only occur at older ages. A trial from the U.S. Maternal-Fetal Medicine Units Network found that treatment of mild GDM did not significantly reduce the frequency of a composite outcome that included stillbirth or perinatal death and several neonatal complications; it did reduce the risks of fetal overgrowth, shoulder dystocia, cesarean delivery, and hypertensive disorders (44). Further research examining the

later consequences of GDM is clearly required, given the strength of observational evidence discussed above.

Another related strategy is to prevent obesity and diabetes in pregnancy. A number of older studies have tried exercise (45), diet (46), or a combination (47). There is evidence of a trend to lower gestational weight gain in the combined interventions, but there was limited effect on GDM and no effects on offspring birth weight or obesity markers in the next generation. The Finnish Gestational Diabetes Prevention Study (RADIEL) trial randomized high-risk pregnant women (prior GDM or obese) using individualized counseling on diet, physical activity, and weight control. Control subjects received standard antenatal care. There was a 39% reduction in GDM incidence among intervention women compared with usual-care women (48). This is the first study to see GDM effects; however, no differences were seen in infant size between groups. There is more to be done here to include interventions that are more effective, as compliance has not always been satisfactory, and with longer offspring follow-up.

Finally, another strategy is to prevent obesity and diabetes in youth. A Cochrane review included 55 studies targeting children 6–12 years of age (49) and found that programs were effective at reducing adiposity, though by only -0.15 kg/m^2 (95% CI -0.21 to -0.09), with substantial heterogeneity between programs in all

age-groups. Several promising policies and strategies included changes in school curriculum that include healthy eating, physical activity and body image, increased sessions for physical activity, improvements in nutritional quality of the school food supply, and others showing that effective programs must be deeply embedded in school culture.

One of our recent contributions in this area aims to reduce risk factors for type 2 diabetes in American Indian youth—the Tribal Turning Point Program (TTPP), a primordial prevention feasibility trial. In this pilot, 60 prepubertal 8- to 10-year-old youth and their caregivers were randomized to a lifestyle intervention or a control condition. The lifestyle intervention had three components, a group-based DPP-inspired active learning curriculum focused on behavior change, toolbox materials, and individual-level motivational interviewing. After 8 months of follow-up with excellent retention, all obesity outcomes substantially and significantly decreased in the intervention compared with control group (50). Given the initial success of the pilot, we are now actively expanding the study and will conduct a fully powered trial with implementation and dissemination components.

IMPLICATIONS FOR FUTURE RESEARCH

To understand better the burden and risk of youth-onset diabetes, the effects of prevention programs, the development and burden of complications, and later mortality, sustainable surveillance will be required, such as conducted by SEARCH, perhaps with expansion for more complete coverage of high-risk minorities.

To explore comprehensively the role of the environmental exposome and its biologic pathways and to identify potentially causal associations, longitudinal (pre)birth cohort studies are crucial. Expansions to consortia, such as The Environmental Determinants of Diabetes in Young (TEDDY) and ECHO studies, and addition of ones specifically targeted at obesity and diabetes prevention are needed.

In order to improve our understanding of mechanisms, animal studies with rapid translation to humans and mechanistic studies nested in population cohorts are robust ways to move our understanding forward more quickly.

Finally, we must focus on breaking the vicious cycle of diabetes and obesity at

multiple levels, with an increased focus on primordial prevention, which will require effective interventions, including randomized clinical trials and translational studies.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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