The SEARCH for risk factors

Professor Dana Dabelea is a researcher with expertise in paediatric diabetes and the developmental origins of chronic diseases. Here, she discusses how she is using a life course approach to generate new knowledge about diabetes.

Can you provide a brief outline of your career and explain how you became interested in researching paediatric diabetes?

I have been engaged in diabetes research for nearly 20 years. I was trained as a physician diabetologist in Romania, where I also completed a clinical science PhD, then went on to work at the medical faculty of Timisoara Medical University in Romania. I spent two years of my postdoctoral studies at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Phoenix, Arizona, Epidemiology Field Studies Branch, where I focused on diabetes research among the Pima Indians. It was there that I became interested in the rising rates of type 2 diabetes in the youth population, and subsequently wrote one of the first papers highlighting this trend. I have also conducted research into diabetes during pregnancy, and became convinced that a life course approach was one that would pay exciting dividends in the future. My particular interest lies in paediatric diabetes research because children have a higher lifetime burden of diabetes than adults. By studying younger people with diabetes, we increase our chances of finding risk factors for the disease – and for disease progression – before chronic complications develop.

How did you become involved in the SEARCH for Diabetes in Youth Study? What are the main objectives of this research?

In 2001, I accepted a junior faculty position at the University of Colorado’s School of Medicine in Denver, USA, in the Department of Preventive Medicine and Biometrics, which became the Colorado School of Public Health in 2008. This allowed me to become involved with the US Centers for Disease Control and Prevention (CDC)/National Institutes of Health (NIH)-funded SEARCH for Diabetes in Youth Study, a multicentre registry and cohort follow-up study of diabetes in youth. I subsequently became the Colorado site’s Principal Investigator in 2003 and the national co-Chair of the steering committee in 2005. This project is now in its fourteenth funded year, and is likely to continue for another five years. SEARCH is the most comprehensive US project addressing the epidemiology, classification and natural history of diabetes in youth, encompassing all the major racial and ethnic groups in the US. It was designed to estimate the prevalence and incidence of diabetes among youth and characterise diabetes-related health outcomes and their risk factors, including barriers to quality healthcare.

What makes Colorado a particularly appropriate place in which to investigate this disease?

Colorado is a large state, contributing the greatest number of cases to SEARCH each year. Given the wide racial and ethnic distribution, it is the largest non-Hispanic white and American Indian source of participants for our study and the second largest source of Hispanic cases. Youth with diabetes are identified from a network of practitioners, health centres and hospitals. All of the large hospital systems in the state participate in SEARCH, at least annually, by providing electronic information and medical record access for validation. One of SEARCH’s major accomplishments has been the establishment of close partnerships with several participating American Indian reservations in the region.

How has SEARCH contributed to the development of clinical and epidemiologic definitions of diabetes?

With the epidemic of obesity and the younger age of onset in both type 1 and type 2 diabetes, the lines between the two major forms of this disease have become blurred. In other words, although most children are accurately diagnosed with either type 1 or type 2 diabetes, a subset of children may have clinical characteristics that overlap between the two, making it difficult for physicians or researchers to easily determine diabetes type. To address this issue, SEARCH has led an effort to improve accurate classification of diabetes in youth by developing clinical and epidemiologic definitions for both types. This endeavour is important, not only for SEARCH but also for clinical purposes, to ensure that all children are accurately diagnosed and given the appropriate treatment.

Where do you see this research taking you in the near future?

There is a pressing need to continue our surveillance efforts. Given the evidence of early complications, despite current therapeutic approaches, the long-term observation of youth with diabetes is necessary to continue advancing our understanding of the disease. SEARCH is therefore planning to continue following up with these young individuals. Furthermore, a significant part of my own research will focus on the primordial prevention of obesity, diabetes and cardiovascular disease.
DIABETES CAN BE divided into two types – both sharing similar features but with different underlying cellular and molecular drivers. Type 1 diabetes usually develops in childhood as the result of an autoimmune attack on insulin-producing islet cells, with patients requiring lifelong insulin injections for survival; while type 2 diabetes generally develops in adulthood following the development of insulin resistance. This variety is associated with obesity, unhealthy diet and lack of physical exercise. Worryingly, the past few decades have seen a substantial increase in the incidence of childhood diabetes, and while type 1 diabetes remains the main form of diabetes in youth under 16, in recent years type 2 diabetes has increasingly emerged among young people in Europe and America.

Until the beginning of the 21st Century, there was very limited reliable data on the burden of paediatric diabetes in the US. In response, a multicentre epidemiological study was launched in the early 2000s to quantify the prevalence and incidence of both types of diabetes in American children and teenagers. This ongoing population-based study – SEARCH for Diabetes in Youth – is completely unique in that it focuses on racially diverse populations and on both types of diabetes.

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SEARCH for Diabetes in Youth is a comprehensive long-term study that gathers data about the prevalence and incidence of diabetes in children. Focusing on racially diverse populations in the US, it is charting key insights into this increasingly common disease.

PINPOINTING THE PATTERNS
To date, SEARCH has made some illuminating insights into diabetes among American youth. For instance, the research team found that the total number of youth with diabetes in the US was at least 154,000 in 2001 and 192,000 in 2009. They also found that approximately 18,000 youth are diagnosed with type 1 diabetes on an annual basis, while 5,000 are diagnosed with type 2 – and the prevalence of both types is still rising: “Worryingly, a recent analysis suggests that given current population projections and observed trends, the number of youth with type 1 diabetes will nearly triple and the number with type 2 diabetes will quadruple by 2050,” Dabelea discloses.

Additionally, SEARCH has highlighted some distressing patterns regarding the clinical presentation and treatment patterns of diabetes among children and youth. For instance, studies have shown that 50 per cent of youth are hospitalised at the onset of diabetes and that approximately 30 per cent of children newly diagnosed with type 1 diabetes present in diabetic ketoacidosis. The researchers have also found strong evidence that suggests diabetic youth are at greater risk of developing kidney disease, retinopathy and heart disease – a trend that is particularly pronounced among those in racial and ethnic minority groups and/or those with type 2 diabetes. “While these findings are troubling, they are also extremely important because they tell us that even at a young age, in a population with short duration of disease,
INTELLIGENCE

SEARCH FOR DIABETES IN YOUTH, EXPLORING PERINATAL OUTCOMES IN CHILDREN AND HEALTHY START

OBJECTIVES

• To establish the prevalence and incidence of diabetes among youth, and to characterise diabetes-related health outcomes and their risk factors, including barriers to quality healthcare

• To explore the role of foetal programming and developmental over-nutrition in the pathogenesis of childhood obesity

KEY COLLABORATORS

Professor Elizabeth J Mayer-Davis, PhD, SEARCH Co-Chair; Professor Anna Maria Siega-Riz, University of North Carolina at Chapel Hill • Professor Lawrence Dolan, MD, Cincinnati Children’s Hospital Medical Center, Ohio • Jean Lawrence, ScD, MPH, Kaiser Permanente Southern California • Professor Catherine Pihoker, MD; Professor Santica Marcovina, PhD, ScD, University of Washington • Professor Ronny A Bell, PhD; Professor Ralph D’Agostino, Jr, Wake Forest School of Medicine, North Carolina • Giuseppina Imperatore, MD, PhD; Sharon Saydah, PhD, US Centers for Disease Control and Prevention, Georgia • Barbara Linder, MD, PhD, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Maryland • Professor Jacob E Friedman, PhD; Professor Richard F Hammman, MD, DrPH; Professor Susan Johnson, PhD; Professor Stephen Daniels; Assistant Professor Tessa Crume, PhD, University of Colorado, Denver

FUNDING

US Centers for Disease Control and Prevention • NIDDK

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we can see risk factors and early signs of chronic complications that will develop later,” Dabelea highlights. “They indicate that we must start programmes to address these increased risks and seek to prevent the development of long-term health problems.”

MAPPING THE MATERNAL LINK

Importantly, Dabelea’s studies have emphasised that maternal diabetes and obesity are associated with type 2 diabetes in youth. Her work among the Pima Indian population in Arizona in the late 1990s found that the offspring of mothers with diabetes had a higher risk of both type 2 diabetes and obesity, providing strong evidence that the intrauterine environment affects obesity and diabetes risk in Pima Indian children. Subsequent SEARCH case control studies among white, black and Hispanic youth identified similar risk patterns in these populations, demonstrating that childhood obesity and diabetes risk has in utero origins across different racial and ethnic groups.

In an effort to understand the metabolic pathways that underpin these risk patterns, Dabelea launched a historical prospective cohort study when she first moved to Colorado in 2001, entitled ‘Exploring Perinatal Outcomes in Children’ (EPOCH). This study has resulted in multiple publications – and the findings to date reveal that the offspring of mothers with gestational diabetes weigh more, have higher levels of subcutaneous and visceral adipose tissue, and have increased cardiovascular risk factors and faster growth trajectories through late childhood. Interestingly, breastfeeding attenuates these long-term consequences.

EPOCH received funding for an additional five years beginning in autumn 2012, which will enable Dabelea and her team to follow the participants through puberty and therefore generate further insights. In yet another longitudinal pre-birth cohort study of 1,400 mother-child dyads, Healthy Start, Dabelea and her team are exploring specific intrauterine mediators responsible for these effects. This study follows mothers from the first trimester of pregnancy through birth, and their offspring to 4-6 years of age, examining the effects of maternal behaviours during pregnancy (including maternal diet, physical activity and smoking), infant and childhood diet, sleeping and feeding practices, and early life growth trajectories, on the development of childhood obesity. Through these studies, Dabelea seeks to enhance knowledge of primordial prevention of type 2 diabetes, with potentially widespread public health implications.

A TIMELY STUDY

In the context of increasing rates of type 1 and type 2 diabetes in children, SEARCH is a unique and timely study that is helping to advance understanding of these chronic diseases and their complications. Indeed, with projections indicating that current trends will worsen, there is an urgent need to investigate the causes of diabetes and explore the social and environmental factors linked to its pathogenesis. To this end, Dabelea will continue her observational studies on the risk factors in pregnancy and early life that lead to increased risk of obesity and diabetes among offspring. In turn, this will lead to the future implementation of clinical trials that test effective interventions to diminish these risks. “We hope that in the next few years, the knowledge provided by our studies will translate into enhanced quality of care and improved quality of life for children with diabetes, and will ultimately lead to the successful prevention of diabetes over the life course,” concludes Dabelea.

SPOTLIGHT ON HEART DISEASE

The risk of developing heart disease is 10 times higher in people with type 1 diabetes compared with the general age-matched population. However, it is not known whether the course of heart disease begins in childhood or adulthood – and knowledge about disease onset is crucial for dictating when preventive therapeutic strategies should begin.

Professor Dana Dabelea has therefore implemented an ancillary study that focuses on a subset of SEARCH children, teenagers and young adults with type 1 diabetes, and a non-diabetic control group from Colorado and Ohio. She has compared the burden of subclinical cardiovascular abnormalities – including carotid intimal-medial thickness, a marker of atherosclerosis and arterial stiffness – between the two groups, in order to pinpoint early signs of preclinical heart disease. The hope is that this research will help build an understanding of when preventive therapeutic strategies should begin.