Results of long-term study could help identify children at risk of future type 2 diabetes

January 23 2020, by Toby Leigh

Researchers at the University of Plymouth and Nestlé have revealed new insights into the factors that predispose children to developing type 2 diabetes in adult life.

The findings have emerged from a unique study, EarlyBird, that followed 300 healthy children in Plymouth, UK, for 15 years to determine who would become at risk of developing type 2 diabetes, and why.

The EarlyBird researchers monitored the children from five years of age to early adulthood to explore how the metabolism changes during growth. The findings, appearing in a series of peer-reviewed scientific publications, have shed new light on the biological and physiological factors that are relevant for metabolic health in childhood.

The latest results, published in *Diabetes Care*, show that the earliest event leading to pre-diabetes (the earliest signs of diabetes) is dysfunction of the pancreatic beta-cell, independent of body weight. Beta-cells in the pancreas produce insulin, the hormone that regulates blood sugar levels. The study also showed that this beta-cell dysfunction was associated with the presence of genetic factors previously associated with type 2 diabetes in adults.

This discovery could lead to the early identification of children that are at high risk of future type 2 diabetes.

Jon Pinkney, Professor of Endocrinology and Diabetes in the University of Plymouth's Peninsula Medical School and Honorary Consultant Physician in Endocrinology and Diabetes at University Hospitals Plymouth NHS Trust said:

"The rapidly rising prevalence of type 2 diabetes is one of the biggest global health challenges, and there is an urgent need to develop effective strategies for early intervention and prevention.

"The research partnership between University of Plymouth and Nestlé has shown how the risks of future type 2 diabetes can be predicted in childhood. This opens up the possibility of individualised advice and early intervention to reduce the risks of future type 2 diabetes."

"In this study we show that beta-cell dysfunction is an early event in the onset of pre-diabetes in children and that this effect is body weight independent",
said François-Pierre Martin, an expert in metabolism who led the collaboration at Nestlé Research.

"However, we also report in this study that subsequent weight gain during puberty aggravates the progression from pre-diabetes to diabetes. This stresses the importance of lifestyle and nutritional interventions in childhood to reduce the risks to develop diabetes."

Jörg Hager, a genetics expert at Nestlé Research who designed the genetic part of the study said:

"Our research has important implications for potentially identifying children at risk of developing pre-diabetes through genetic markers. The new findings will allow us to develop new nutritional approaches that target the insulin response to a meal, and the body's ability to regulate blood sugar level."

Begun in the early 2000s, when the obesity epidemic was still in its infancy and the idea that children could develop type 2 diabetes almost unheard of, EarlyBird was able to develop strong relationships between families and researchers and retain a high proportion of children over the course of the study.

The detailed metabolomic and genetic data collected over such a long period of childhood are unique. As a consequence, researchers have been able to make a number of vital discoveries about the relationships between lifestyle, genetics and health.

The EarlyBird study

The EarlyBird study was set up in the year 2000 by Professor Terry Wilkin and Dr. Linda Voss, at a time of increasing childhood obesity and the emergence of type 2 diabetes in adolescents. Insulin resistance is thought to underlie the development of type 2 diabetes and the aim of the study was to determine which children became insulin resistant and why.

A cohort of over 300 healthy five-year-olds and their parents was recruited. DNA samples were taken from both children and parents at baseline. Thereafter, the children were followed-up every six months until the age of 16 years.

Six-monthly measurements included:

- anthropometry (height, weight, waist circumference, percentage fat by bioimpedence)
- blood pressure
- general and family health updates

Annual measurements included:

- body composition (DEXA)
- resting energy expenditure, heart rate variability, arterial tonometry
- physical activity (accelerometry)
- dietary choice (food frequency questionnaire)
- pubertal stage (Tanner self-report and objectively by first detection of LH and age at peak height velocity)
- biochemical blood measures (fasting glucose, insulin, lipid profile, hsCRP, γGT, adiponectin, leptin); blood counts (full haemogram, HbA1C, SHBG); hormonal markers (IGF-1, LH, FSH, AMH, androgens)
- Key findings include trends and associations of insulin resistance and metabolic risk factors in childhood, physical activity and its relationship to obesity and metabolic risk, early life programming of obesity and metabolic risk, gender differences in metabolic risk during childhood and beta cell function in children who developed impaired fasting glucose.

The study has had worldwide recognition, with over 60 associated publications to date, as well as being featured numerous times in the media and discussed in the House of Lords.

The Plymouth EarlyBirds as adults

Built upon the foundations of the previous study, this unique childhood cohort has now been followed up into adult life, in order to investigate the longer-term implications for health of the metabolic variations and trends already observed from ages 5–16 years.

The new study, led by Professor Jon Pinkney and Dr. Joanne Hosking, is designed to test the principal hypothesis that defective pancreatic beta cell function persists from childhood into adult life and is associated with distinctive patterns of gene methylation and metabolomic profiles

that may be first detected during childhood.

The impact of epigenetic and metabolomic profiles on a wide range of phenotypic characteristics, including adiposity and body composition, will also be investigated. The new study repeats core measurements of the EarlyBird study using the same methods, but while incorporating several new measures, some other measurements at earlier ages will not be repeated.

More information: Jerome Carayol et al. Genetic Susceptibility Determines β-Cell Function and Fasting Glycemia Trajectories Throughout Childhood: A 12-Year Cohort Study (EarlyBird 76), *Diabetes Care* (2020). DOI: 10.2337/dc19-0806

Provided by University of Plymouth