10 YEARS:
10 STORIES OF IMPACT

CASE STUDY 2

ENDIA: a world-first study investigating environmental triggers of islet autoimmunity from as early as pregnancy

The development of type 1 diabetes (T1D) results from interactions between T1D-susceptibility genes and the environment, and this interplay likely starts very early in life. Despite significant global investment in this area, environmental factors affecting the development of T1D are not yet confirmed or well understood.

The Australian Type 1 Diabetes Clinical Research Network (T1DCRN) has funded a world-first project, Environmental Determinants of Islet Autoimmunity (ENDIA), to examine the origins of islet autoimmunity in children from as early as during pregnancy. The project has attracted significant leveraged funding and is being replicated globally. The ENDIA team is collaborating closely with international researchers, aiming to identify environmental exposures that trigger islet autoimmunity and thus would present ideal therapeutic targets for the prevention of T1D.

Australian Type 1 Diabetes Clinical Research Network

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WHAT PROBLEM DO WE NEED TO SOLVE?

In Australia, T1D in children is more than twice as common as it was 30 years ago.[7] The fact that the incidence of T1D has increased so significantly suggests a strong influence of environmental factors acting on genetic susceptibility.

While the condition can occur at any age, cohort studies of at-risk children, including ENDIA, indicate that T1D associated autoantibodies can be present from the first year of life[8], and peak in the second year of life, and that those who develop T1D at a young age have a more aggressive form of the condition.[9]

This corroborates the hypothesis that environmental exposures in early life contribute to T1D risk, whether related to maternal influences on the foetus during pregnancy, neonatal factors, or later effects during infancy and early childhood.

Interestingly, studies show that maternal T1D during pregnancy offers protection against development of the condition compared to the higher risk of T1D if the babies' father or a sibling is diagnosed, a phenomenon called maternal protection.[10]

Yet we do not yet know what starts the immune activation causing the destruction of beta cells in individuals susceptible to T1D, and why the rate of progression varies so significantly between people. Answers to these questions would substantially assist efforts to prevent the development of T1D.

WHAT WAS FUNDED BY THE T1DCRN, AND WHY?

In 2012, **Professor Jennifer Couper** (University of Adelaide) along with **Professor Leonard Harrison** and a team of multidisciplinary experts across Australia, determined that a long-term study collecting data on 'omics' biological systems, genetics and the environment going back to the mothers in pregnancy was needed to investigate the prenatal and early-life exposures responsible for driving the development of islet autoimmunity.

The Environmental Determinants of Islet Autoimmunity (ENDIA) study was then commenced, the world's first and largest study examining the origins of autoimmunity in children from as early as pregnancy. As recruitment progressed, the potential for ENDIA to make significant discoveries in the origins of T1D became apparent and the project was extended with funding from the T1DCRN in 2014.

ENDIA is a pioneering effort examining how the modern environment is contributing to the increase in childhood T1D from as early as the foetal stage of life. It is uniquely positioned to identify how genes and the environment interact from pregnancy through early childhood to drive or protect against the development of islet autoimmunity, an early sign of the initiation of T1D.

With sustained funding through the T1DCRN and other leveraged funders, including the Leona M. and Harry B. Helmsley Charitable Trust (Helmsley), ENDIA has been in operation for almost a decade, recruiting 1,500 participants who have an immediate family member with T1D and monitoring them prospectively from pregnancy into early childhood.

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7. Penno MA, et al. Environmental determinants of islet autoimmunity (ENDIA): a pregnancy to early life cohort study in children at-risk of type 1 diabetes. BMC Pediatr. Aug 14 2013;13:124. doi:10.1186/1471-2431-13-124

8. ibid.

9. Leete P, et al. Studies of insulin and proinsulin in pancreas and serum support the existence of aetiopathological endotypes of type 1 diabetes associated with age at diagnosis. Diabetologia. 2020/06/01 2020;63(6):1258-1267. doi:10.1007/s00125-020-05115-6

10. Larsson PG, et al. Previous maternal infection protects offspring from enterovirus infection and prevents experimental diabetes development in mice. Diabetologia. Apr 2013;56(4):867-74. doi:10.1007/s00125-013-2834-z

WHAT HAS THIS PROJECT DELIVERED AND WHY IS IT IMPORTANT?

The impacts of ENDIA to date are far reaching, including providing:

1 A rich collection of biosamples

To date, the ENDIA study has collected over 167,000 biosamples including immune cells, breast milk, nasal swabs, stool, and urine samples, providing information on various factors such as infection history, nutrition, immune profiles, and lifestyle (see Figure 1 below).

The ultimate aim is to determine if there are indicators in these samples which may be associated with development of islet autoimmunity and T1D.

2 An invaluable data set

The biosamples collected through ENDIA provide data from years of monitoring and collection, ethical approval processes, and recruitment of participants. The invaluable datasets generated during the study are now available to researchers all over the world. The global nature of ENDIA allows researchers to access expertise which is not available in Australia, amplifying the impact of the study towards effective strategies for preventing T1D.

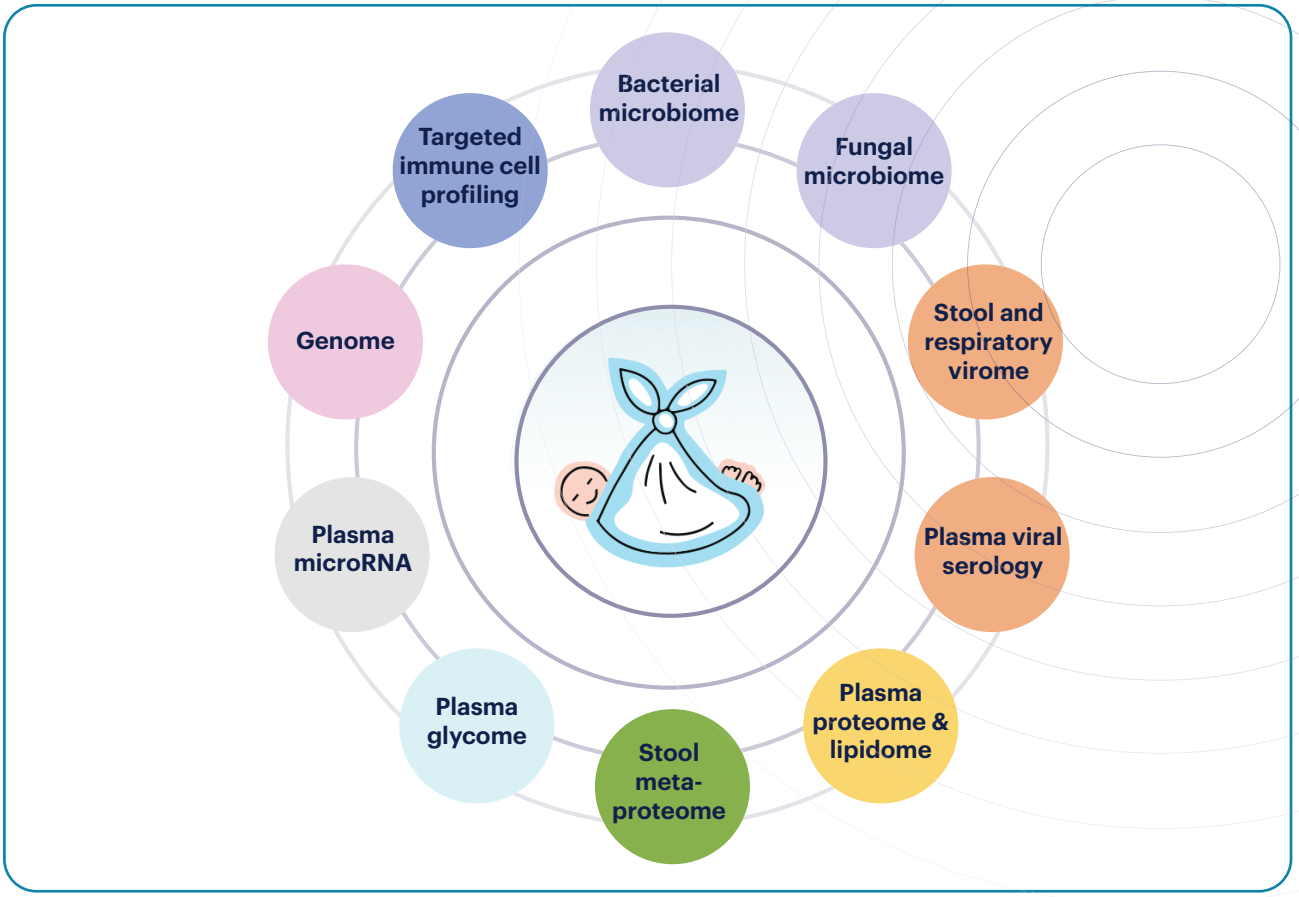

Figure 1: ENDIA samples are currently being used for a variety of investigations. For example, the samples are being used to determine the link between 'omics' exposures and islet autoimmunity (adapted from image provided by ENDIA team).

> The ENDIA study's over-arching purpose is to develop treatments to prevent childhood T1D, and over the past 10 years has brought together expertise in Australia to provide the best chance of discovering what drives T1D in early life.
>
> **Professor Jennifer Couper,** Principal Investigator of ENDIA

3 Novel understanding about T1D triggers

Already, ENDIA has led to 22 scientific publications that are having a major impact on understandings of new triggers for T1D and uncovering novel genetic links.

New discoveries include:

- T1D during pregnancy leads to significant changes in the gut microbiome **(Professor Leonard Harrison)**[11]
- mothers with T1D, and their infants, have a distinct gut viral profile **(Professor Maria Craig and Dr Ki Wook Kim)**[12,13]
- children with T1D have a smaller, less functional pancreases, also observed in children who are in the pre-symptomatic stages of T1D (Professor Jennifer Couper)[14,15]
- some children who develop islet autoimmunity demonstrate a surge in cytokines normally associated with intestinal infection around the time of autoantibody development (ENDIA team)[16]

11. Roth-Schulze AJ, et al. Type 1 diabetes in pregnancy is associated with distinct changes in the composition and function of the gut microbiome. Microbiome. 2021;9(1):167-167. doi:10.1186/s40168-021-01104-y

12. Kim KW, et al. Higher frequency of vertebrate-infecting viruses in the gut of infants born to mothers with type 1 diabetes. Pediatr Diabetes. Mar 2020;21(2):271-279. doi:10.1111/pedi.12952

13. Wook Kim K, et al. Distinct Gut Virome Profile of Pregnant Women With Type 1 Diabetes in the ENDIA Study. Open Forum Infect Dis. Feb 2019;6(2):ofz025. doi:10.1093/ofid/ofz025

14. Augustine P, et al. Pancreas size and exocrine function is decreased in young children with recent-onset Type 1 diabetes. Diabet Med. Aug 2020;37(8):1340-1343. doi:10.1111/dme.13987

15. Penno MAS, et al. Changes in pancreatic exocrine function in young at-risk children followed to islet autoimmunity and type 1 diabetes in the ENDIA study. Pediatr Diabetes. Sep 2020;21(6):945-949. doi:10.1111/pedi.13056

16. Harrison LC, et al. A surge in serum mucosal cytokines associated with seroconversion in children at risk for type 1 diabetes. Journal of Diabetes Investigation. 2023;n/a(n/a)doi:https://doi.org/10.1111/jdi.14031

Using cutting-edge technologies, other studies are also investigating the connection between changes in mothers' gut function and microbiota during pregnancy **(Associate Professor Emma Hamilton-Williams)**, proteins and metabolites in the blood during pregnancy and early life **(Dr Megan Penno)**, and the direct association between the environmental factors and genes disrupted before and during autoimmune progression **(Professor Simon Barry)**.

4 New therapeutic targets

These findings are helping to identify new therapeutic strategies for the prevention of islet autoimmunity. Combined with expanded understandings about how and when immunity is progressing in children, these discoveries will guide the best prevention approaches to test in pregnancy and during the first years of life to decrease a child's risk of developing T1D.

5 Increased collaboration in Australia and globally

The ENDIA study is globally respected for its uniqueness and quality of scientific design. It is being used as an example to apply across other countries, driving the establishment of a consortium which investigates the role of early life events in the origins of T1D.

Already, it has brought together multidisciplinary expertise across Australia and internationally, with a shared goal of understanding and ultimately preventing T1D. This includes connecting researchers from 24 clinical sites and 15 medical research institutes.

6 Immediate benefits for participants

Involvement in ENDIA is also bringing immediate benefits for many of the families who participate. So far, 21 children have been diagnosed with T1D. Further, 33 have been identified with persistent multiple islet autoimmunity, and 34 have been identified with persistent single islet autoimmunity, both of which are markers of pre-symptomatic T1D (Stage 1 and Stage 2).

Each of these 88 children has or will avoid significant illness or diabetic ketoacidosis (DKA) at the point of diagnosis, thanks to close monitoring of T1D progression made possible through ENDIA.

"We wanted to get involved in ENDIA because we hoped it would help find a cure for our son Julian, and that it could help prevent our additional three children – and all children – from ever being diagnosed.

Life with T1D is never easy, and in fact sometimes it gets harder the longer you have had your child living with it. But being able to give back to the community, and hopefully help create a future with no T1D, is something our family is proud to be a part of.

Damian McLeod, father of four, including 11-year-old **Julian** who lives with T1D. He and his wife, **Angela,** have been involved in ENDIA since the birth of their second child, with their three youngest children participating in the study.