ENDIA:

Environmental Determinants of Islet Autoimmunity

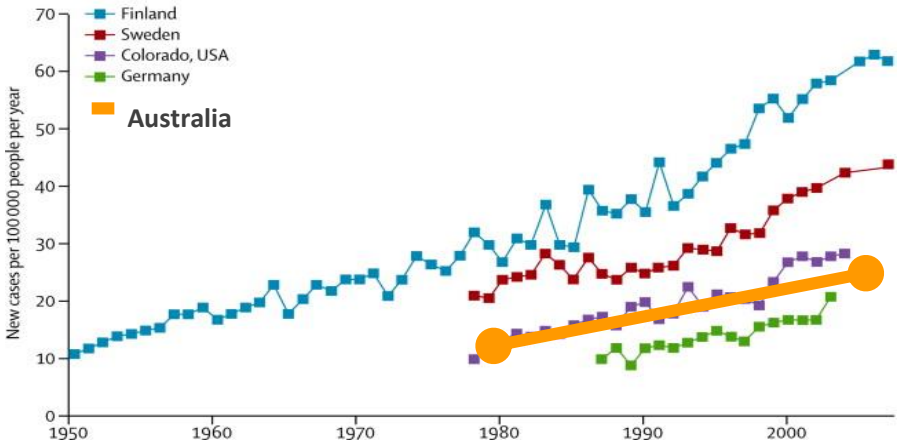
Julianne Wilson and Emma Brownrigg

About the ENDIA Study

- **WHY** do we need ENDIA?
- **WHAT** environmental factors have been implicated in T1D development?
- **WHO** can become involved in ENDIA?
- **WHERE** is ENDIA happening?
- **HOW** are families in ENDIA followed?
- **WHEN** will we have results?

WHY do we need ENDIA?

- Around 122,300 Australians are living with T1D
- Incidence increasing worldwide; doubled in Australia in last 20-30 years
  - 1980s: ~11 per 100,000 head of population aged 0-14 diagnosed every year
  - 2006: 21.7 per 100,000 head of population (0-14 years)
  - 2014: 25 per 100,000 population (0-14 years)
  - Fastest relative rate of increase seen in under 5s
  - Indicative of role of modern environment



Modified from: Atkinson, *The Lancet* 2014

WHY do we need ENDIA?

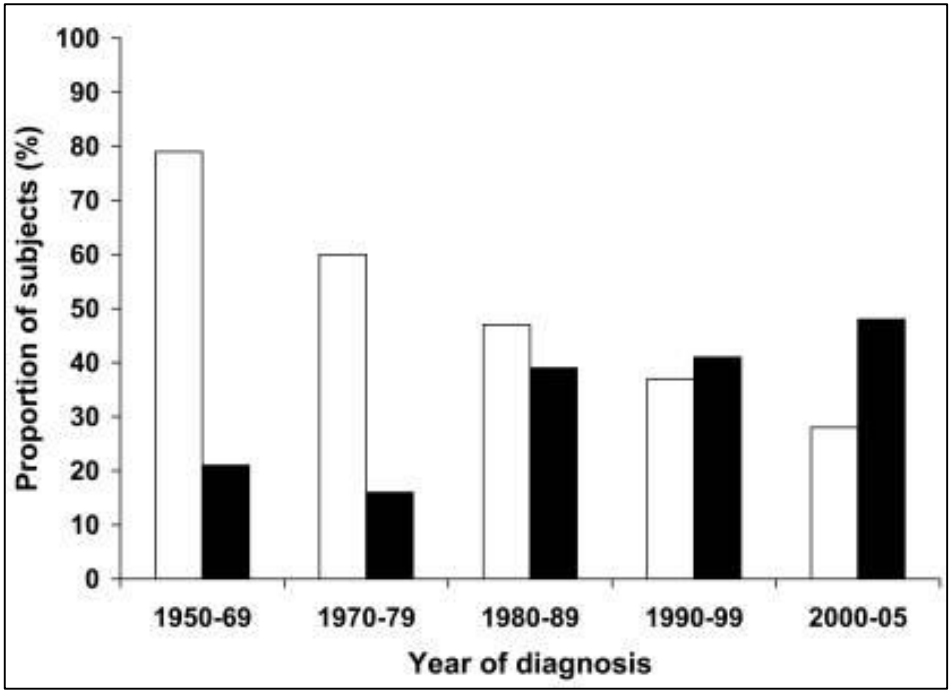
International indicators of an environmental role:

Less than 40% concordance of T1D in monozygous twins

WHY do we need ENDIA?

International indicators of an environmental role:

Reduced relative frequency of high risk genotypes in newly diagnosed over past decades



Fourlanos, Diabetes Care 2008

WHY do we need ENDIA?

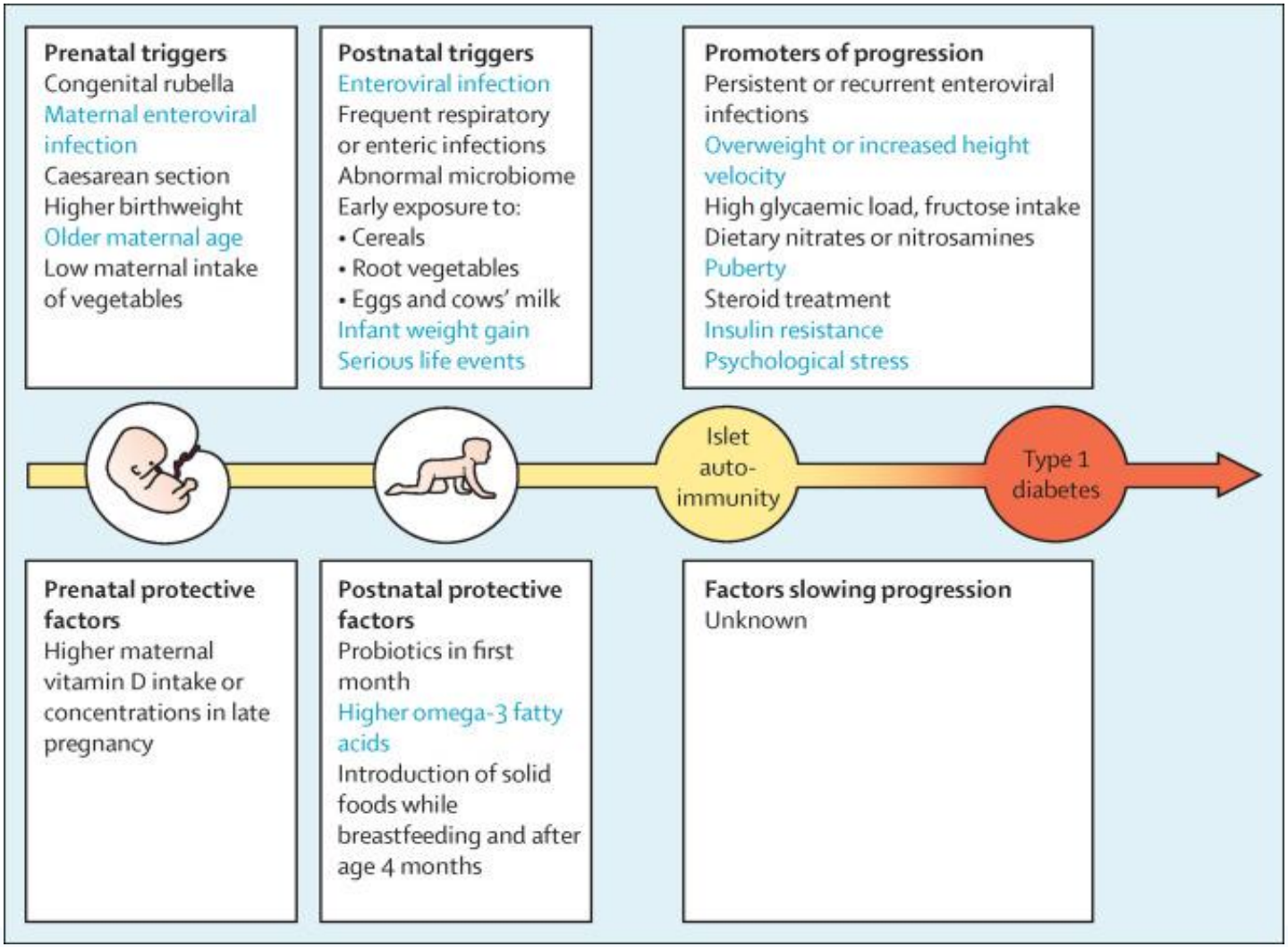
International indicators of environmental role:

Genetically similar populations living in different regions have different incidence rates of T1D

Cases/100,000/year (<15 years)

(Mickael Knip, 2014)

WHAT environmental factors are implicated?

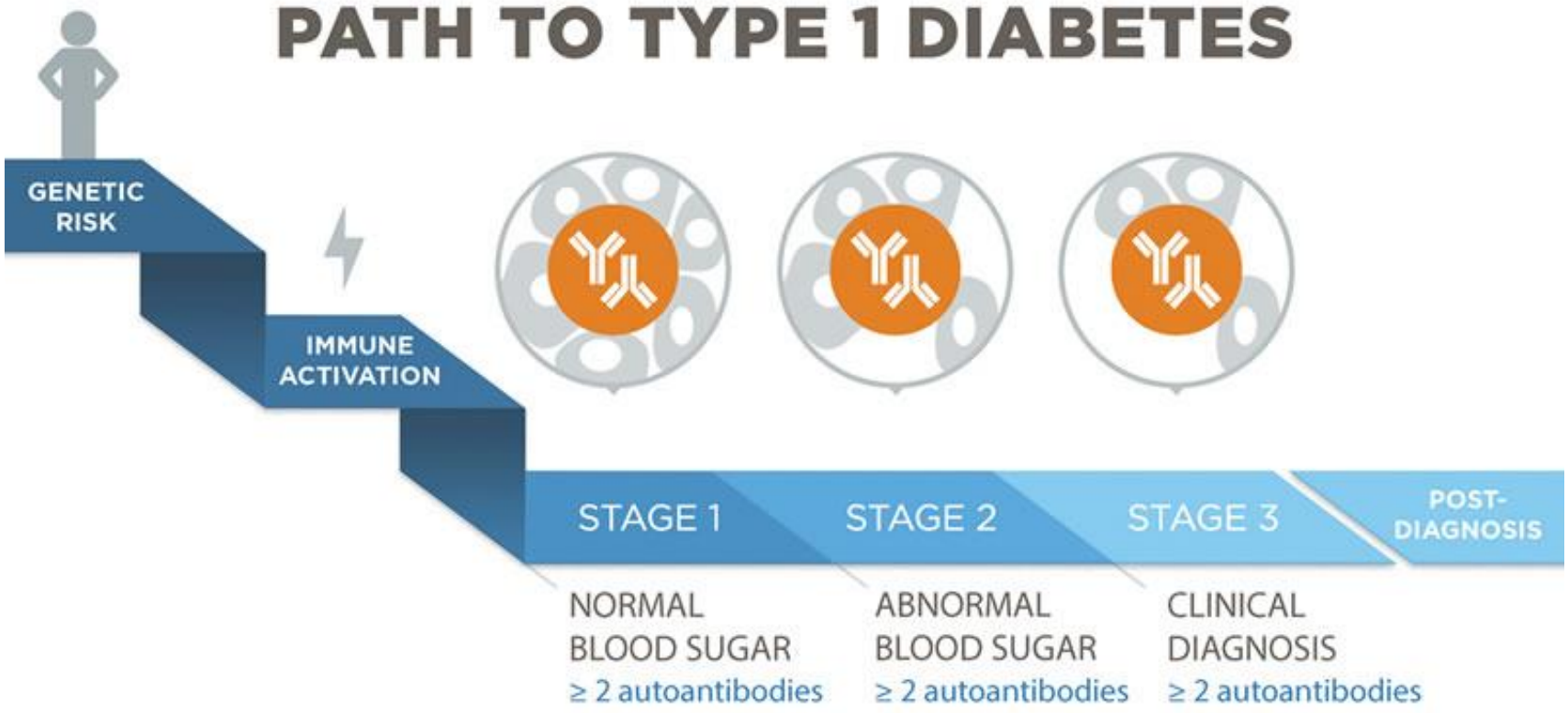


Rewers & Ludvigsson, Lancet, 387(10035), 2016

What is Islet Autoimmunity?

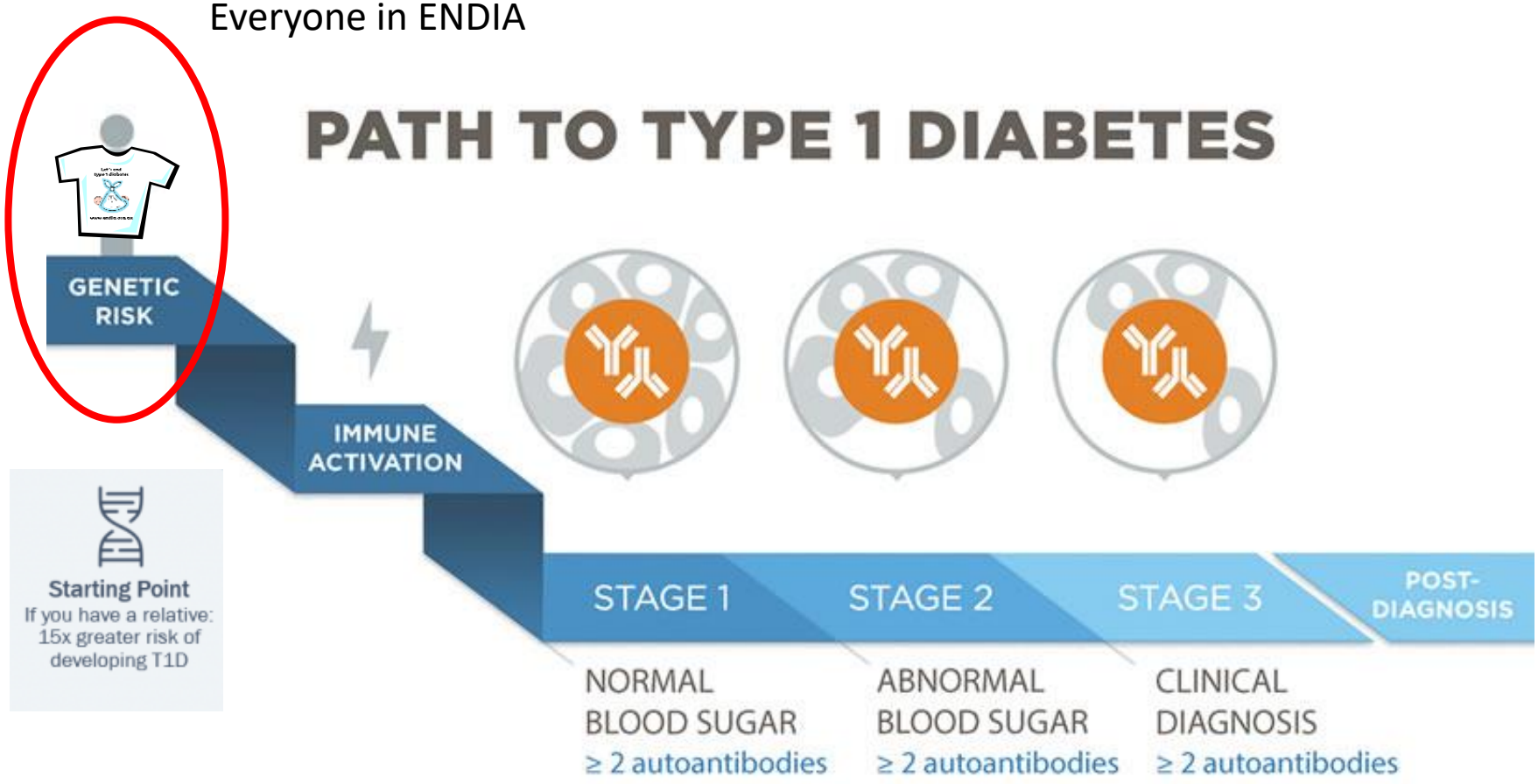
- Type 1 diabetes results from an autoimmune response; the body's immune system destroys its own insulin-producing beta cells in the pancreas.

- Before type 1 diabetes presents with symptoms, this autoimmune response can be detected by measuring antibodies in the blood stream. These antibodies are known as islet autoantibodies and the condition is known as "islet autoimmunity".



https://www.trialnet.org/t1d-facts/stages-of-t1d/stage-1

Everyone in ENDIA



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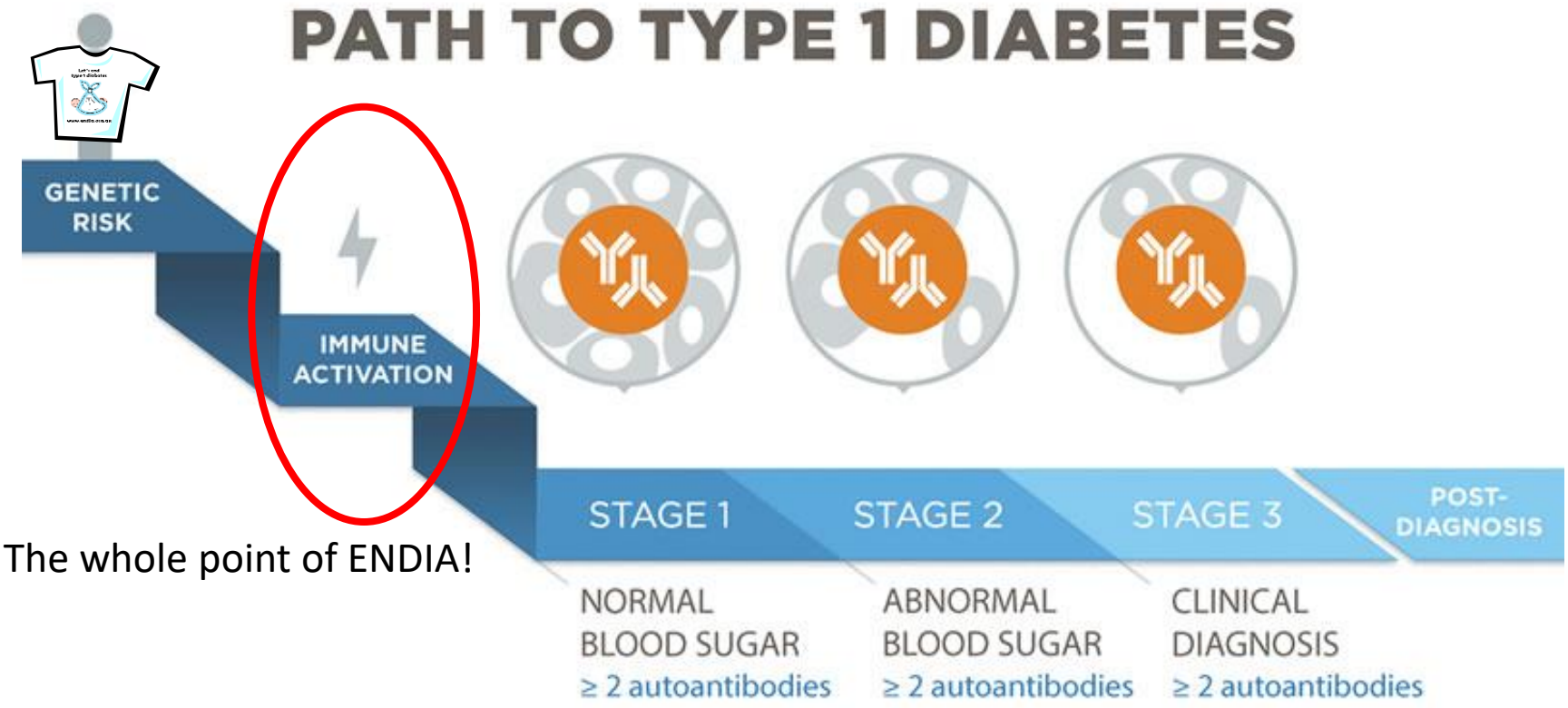
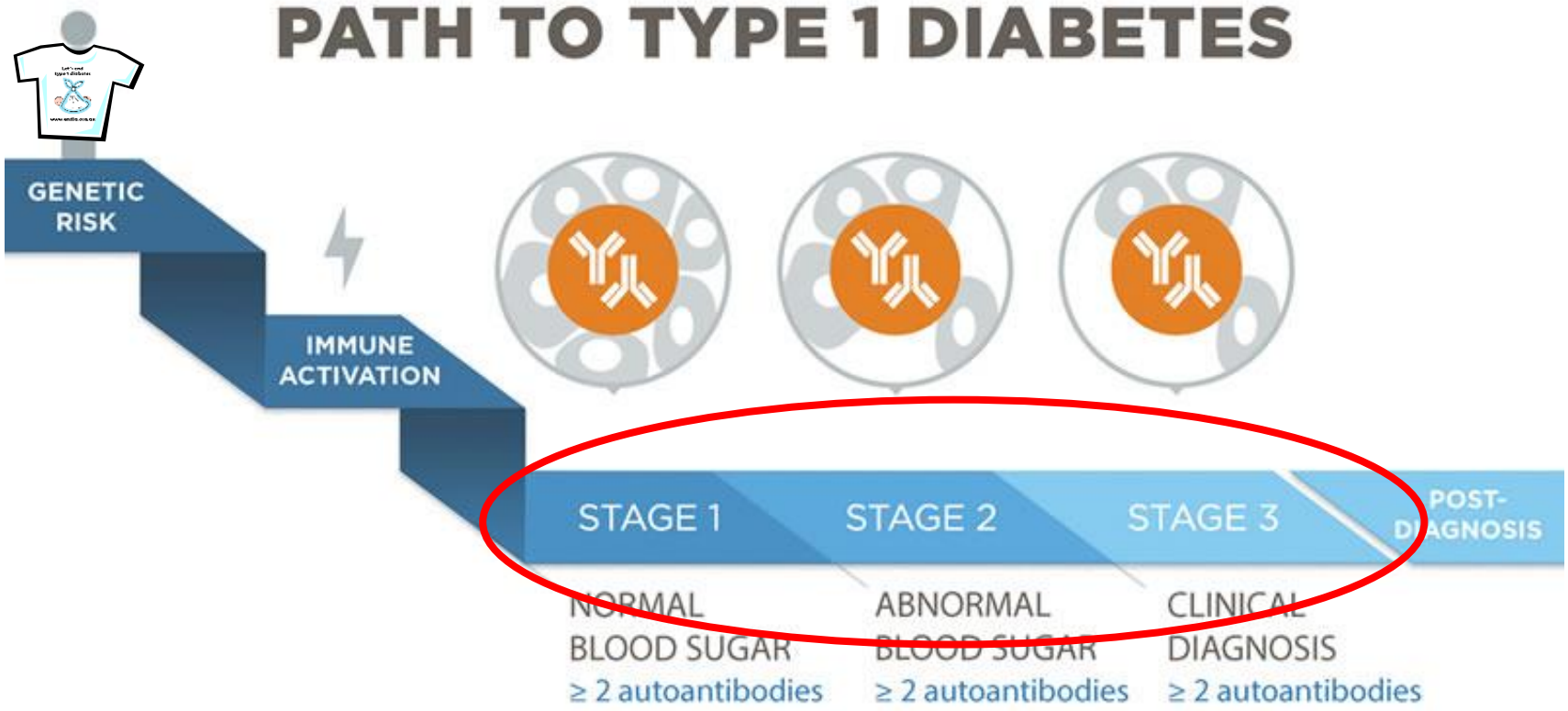


The whole point of ENDIA!

https://www.trialnet.org/t1d-facts/stages-of-t1d/stage-1

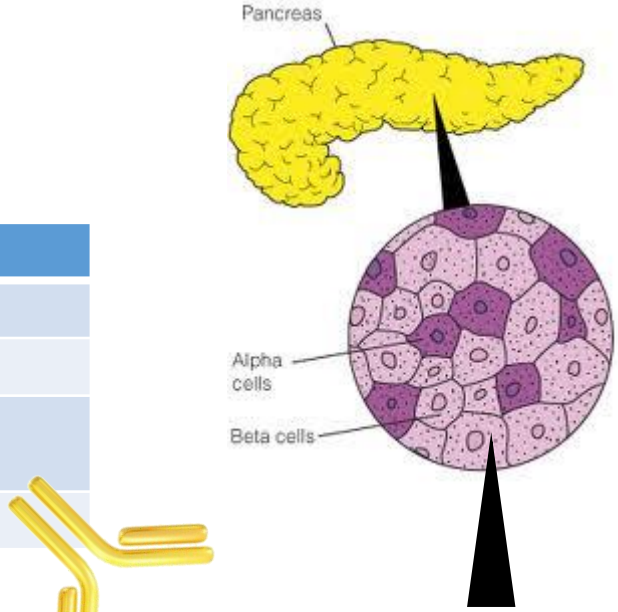


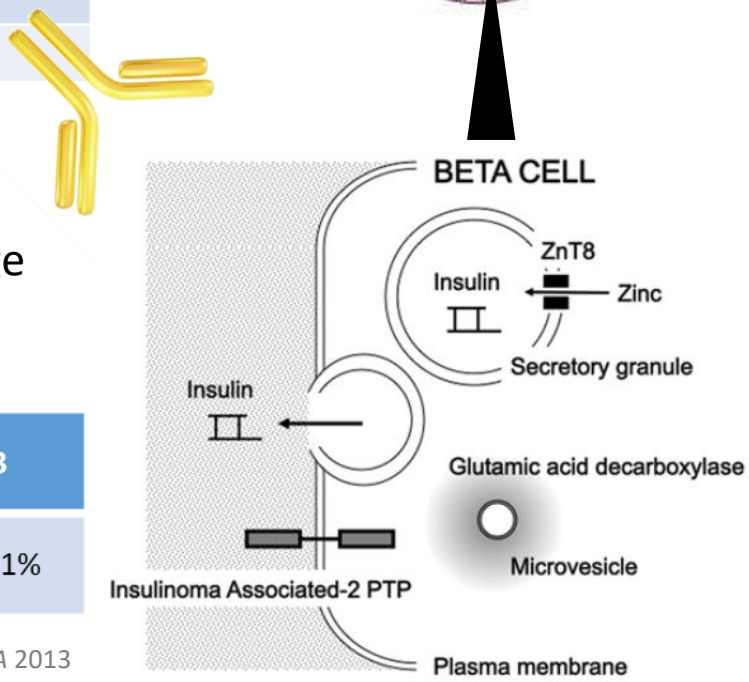
What drives this process?

https://www.trialnet.org/t1d-facts/stages-of-t1d/stage-1

- Primary outcome: ≥2 detectible islet autoantibodies over two consecutive visits

Antibody Acronym	Full protein name
IAA	Insulin antibody
GADA	Glutamic acid decarboxylase antibody
IA-2A	Insulinoma associated-2 antibody (a protein tyrosine phosphatase)
ZnT8A	zinc transporter 8 antibody





- Based on Australian BabyDiab study, ~8% of participating children will develop IA with average onset at 2.2 years [Couper, *Diabetes Care* 2009]

Number of islet autoantibodies	0	1	2	3
Risk of developing T1D by 15 years	0.4%	12.7%	61.6%	79.1%

Ziegler, *JAMA* 2013

AIMS of the ENDIA Study

ENDIA is the only prospective study to explore the environmental triggers of type 1 diabetes from **pregnancy** into childhood… in the WORLD

- To recruit and follow 1400 babies from the pregnancy who have a first degree relative with T1D
- To identify the environmental exposures that promote the development of T1D
- To explore how a person's genes can make different environmental exposures important
- To identify factors in the environment which may protect against T1D development

WHO can participate in ENDIA?

Who can participate?

Do you fit into one of the four categories below? If the answer is YES then your family may be eligible to participate in ENDIA – Australia's only pregnancy/birth cohort study looking at the causes of Type 1 Diabetes:

1400 babies required

1

A pregnant woman with Type 1 Diabetes

2

A pregnant woman whose unborn baby's father has Type 1 Diabetes

3

Pregnant women with an existing child that has Type 1 Diabetes who will be a sibling of the expectant baby

4

A baby less than 6 months of age that has a parent or sibling with Type 1 Diabetes

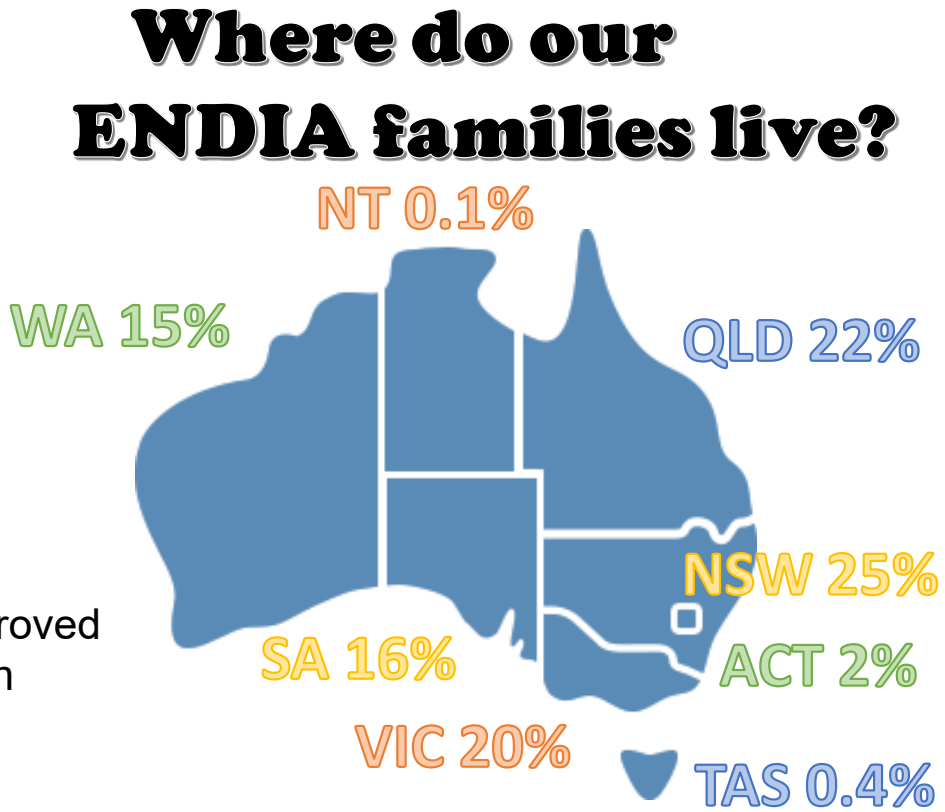
WHERE is ENDIA happening?

ENDIA lead sites include:

- Women's and Children's Hospital, SA
- Princess Margaret Hospital, WA
- Royal Melbourne Hospital, VIC
- Monash Health, VIC
- Barwon Health, VIC
- Children's Hospital at Westmead, NSW
- Royal Hospital for Women, NSW
- St George Hospital, NSW
- Mater Health Service, QLD

Around 30 additional 'satellite sites' approved across Australia for recruitment and birth activities.

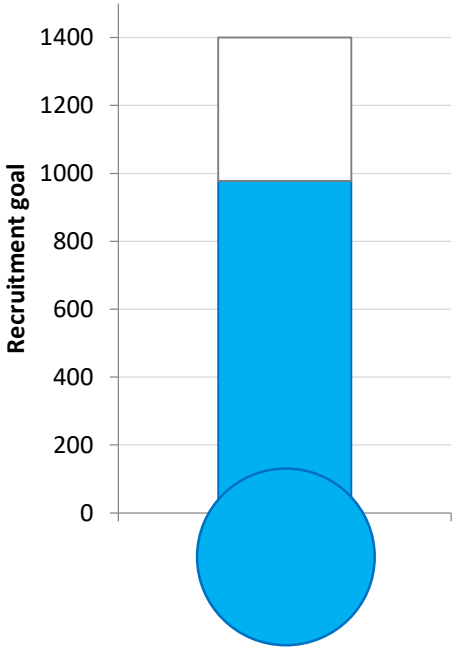
Regional participation program (anywhere else in Australia!) where participants join from home by phone, e-mail, online apps, reply-paid post and courier.



WHERE is ENDIA happening?

121 families with 2 or more children enrolled (5 with 3!) 14 pairs of twins

Recruitment as of 5th April 2018



TOTAL	NSW	VIC	QLD	SA	WA	Regional
978	211	215	184	143	138	85

70%

of target

HOW families in ENDIA are being followed

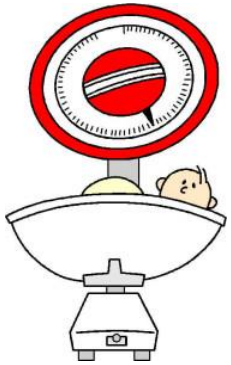
HOW families in ENDIA are being followed

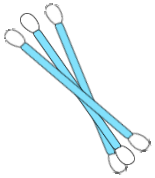
Questionnaires

Preconception
Family demographics & medical history
Diet (pregnancy, breastfeeding & baby)
Lifestyle during pregnancy & early life
Infant health

Assessments

Mother & Father's BMI
Baby's weight, length/height, waist





Samples

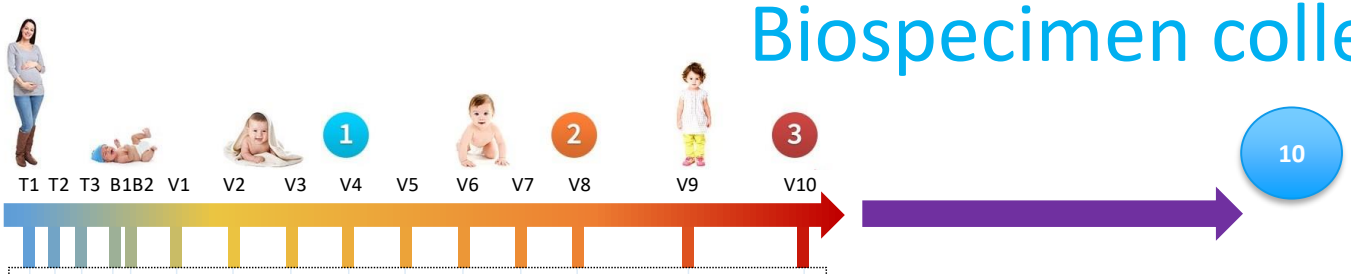
Mother – Urine, Stool, Saliva, Breast milk, Swabs (mouth, nose, skin, vagina)

Baby – Urine, Stool, Saliva, Swabs (mouth, nose, skin)

Placenta & Cord Blood

Other family members – Saliva, Blood, Stool

Biospecimen collection

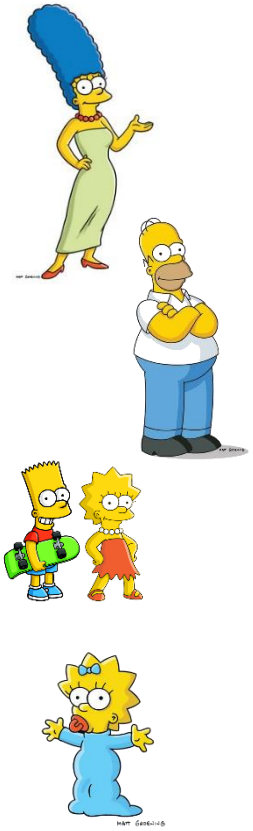


Mum
- *Saliva*
- *Blood (PBMCs)*
- *Stool*
- *Urine*
- *Nasal/oral swabs*
- *Skin swabs*
- *Vagina swab*
- *Breast milk*

Dad
- *Saliva*
- *Blood (PBMCs)*
- *Stool*

Sibling
- *Saliva (all)*
- *Blood (PBMCs; all)*
- *Stool (closest age)*

ENDIA baby
- *Placenta/cord*
- *Blood (PBMCs)*
- *Stool*
- *Urine*
- *Nasal/oral swabs*
- *Skin swabs*
- *Saliva*
- *Spit up*



Key

× Measurement taken at single time point

●–● Measurement taken once during timeframe

Scientific investigations

- Impact of maternal T1D during pregnancy and postnatally
  - Maternal-infant dynamics of the bacterial and fungal microbiomes in pregnancy and early life, and the effect of maternal T1D
  - Maternal-infant dynamics of the gut virome in pregnancy and early life
  - Comparison of nutrition in pregnant women with and without T1D against Australian dietary guidelines
  - Feeding practices of ENDIA infants
  - Method development projects in metabolomics and molecular immunology
- Studies of influence of gestational and early life exposures/'omics on islet autoimmunity from 2019

When will we have all the answers?

The ENDIA Study has been ongoing for over 5 years since 2013.

- The median age of children followed up is around 19 months; but we are still in recruitment phase.
- Once recruitment is complete (some time in 2019), we will be able to report on the full complement of pregnancy data around 12 months on.
- We aim to follow all participants until they reach at least 3 years of age.
- The most common age of diagnosis is around 10-14 years old.

Longer than a pregnancy, longer than a PhD, longer than the course of primary school…

What have we found so far?

Microbiome (bacteria inhabiting our body)

- Stool samples in pregnancy and from baby have shown for the first time that mothers with T1D have different bacteria in their guts, that the baby shares, after the first year of their life (compared to mums without T1D)

Virome (viruses co-inhabiting our body)

- stool samples in pregnancy and from the baby show that for the first time mothers with T1D have different types of viruses and these are transmitted to the baby (compared to mums without T1D).

Children of mums with T1D have the lowest risk (2%) of getting diabetes, so are these gut bacteria and viruses in some way beneficial for the baby??

The 2018 ENDIA Team

ENDIA

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Participating Researchers:

Supported by:

Type 1 Diabetes TrialNet

TrialNet

What is TrialNet?

Type 1 Diabetes TrialNet is an international group of researchers who are exploring ways to prevent, delay and reverse the progression of type 1 diabetes

TN01 Pathway to Prevention Study

- What causes type 1 diabetes and what might predict the development of the disease?
- Provides close monitoring to individuals "at risk" for developing type 1 diabetes
- Clinic visits located at Mater Campus, South Brisbane
- Remote screening offered state-wide.
- Individuals at greater risk may be offered an opportunity to participate in a prevention study

TN01 Pathway to Prevention – Eligibility

- Relatives between 1 and 45 years of age who have a sibling, child, or parent with type 1 diabetes
- Relatives between 1 and 20 years of age who have a cousin, aunt, uncle, niece, nephew, half sibling or grandparent with type 1 diabetes

TN01 Pathway to Prevention – Screening

Two parts:

Screening – involves a blood test for diabetes related autoantibodies. If negative, participants can be screened annually until 18yrs. Once 18, if ab negative, considered 'low risk' for life

Monitoring – if ab positive at screening, pt offered participation in monitoring phase. Baseline visit (OGTT) conducted to determine how regularly participant will be followed up

Type 1 Diabetes TrialNet

TrialNet
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