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Islet autoimmunity in young First Nations women with prediabetes and type 2 diabetes

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ABSTRACT

Aims: Type 1 diabetes in First Nations peoples is low yet type 2 diabetes is at epidemic proportions. This study aimed to determine the prevalence of islet autoimmunity in First Nations women with dysglycaemia and its association with clinical features.

Methods: One hundred and eighty First Nations women with prediabetes (n = 51) or type 2 diabetes (n = 129) were screened for any of GAD, IA-2 and ZnT8 autoantibodies using 3Screen ELISA, then ELISA for individual autoantibodies for positive screens. Associations between individual antibody positivity and clinical and metabolic characteristics were assessed.

Results: Of the 180 women, 16% were positive on 3Screen, comprising 10/51 with prediabetes and 18/129 with diabetes. Sixteen of 28 positive on 3Screen were also positive for at least one individual autoantibody on ELISA testing; with 5/51 (10%) with prediabetes and 11/129 (9%) with diabetes. Individual autoantibody positivity was not associated with clinical and metabolic characteristics or markers of inflammation.

Conclusions: The proportion of individual autoantibody positivity among younger First Nations women with prediabetes or type 2 diabetes was 9%. Islet autoantibody positivity was not associated with a distinct clinical phenotype in this group. Longitudinal follow-up will allow assessment of glycaemic trajectories and clinical outcomes in younger First Nations women.

Terminology

First Nations peoples – Inclusive of Aboriginal and Torres Strait Islander peoples in Australia and Indigenous peoples outside of Australia.

1. Introduction

Islet autoantibodies are associated with immune-mediated beta cell destruction and type 1 diabetes. Genetic susceptibility and environmental triggers drive autoimmunity and affect a population's susceptibility to type 1 diabetes [1]. First Nations peoples have inhabited continental Australia for over 60,000 years and have a unique genome [2], with a lower prevalence of HLA-DR3 and DR4 risk alleles [3] which

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are known to confer susceptibility to type 1 diabetes in European populations [1]. Despite colonisation and massive upheavals, many First Nations peoples in the Northern Territory (NT) continue to live in contiguous cultural groups. Australian studies from the 1980 s [4–6] and data from First Nations peoples in the United States [7], Canada [8] Alaska [9] and New Zealand [10] show type 1 diabetes to be uncommon among First Nations peoples. Despite rising type 1 diabetes incidence in First Nations children in Australia [11], an NT study found that type 1 diabetes accounts for only 0.17 % of all diabetes cases [12]. The difference in incidence of type 1 diabetes in First Nations peoples between the NT and wider Australia is likely due to differing colonisation histories, genetic admixtures, and environmental exposures. Some First Nations populations have possibly inherited high-risk type 1 diabetes alleles from colonising populations amid concurrent, rapid environmental changes. Relevant environmental-biological interactions include obesity, with associated upregulation of proinflammatory innate and adaptive immune reactivity, and changes in the gut microbiome with tissue barrier dysfunction and activation of the immune system [13].

Of most concern is the epidemic of type 2 diabetes, especially among females, with rates in NT First Nations adults and youth among the highest recorded globally [12,14]. Increasing rates of type 2 diabetes in pregnancy [15] and the rapid progression from gestational diabetes (GDM) to type 2 diabetes [16] are considered central to the development of an intergenerational epidemic of type 2 diabetes in this population. Internationally, diabetes heterogeneity is increasingly appreciated [1,13,17], with between 4 % and 14 % of type 2 diabetes populations testing positive for autoantibodies usually linked with type 1 diabetes [18–22], though First Nations peoples are underrepresented in these studies. A 1979 study among 46 Akimel O'odham people (Pima Indians) newly diagnosed with diabetes, reported two participants with islet cell antibodies (ICA) of low titre. On retesting several years later ICA were not detected [23]. A later study involving Akimel O'odham people with type 2 diabetes did not identify any classical type 1 diabetes-associated antibodies but reported several novel autoantibodies associated with insulin secretion [24]. In the Australian Fremantle Diabetes Study from 2000, 3/18 First Nations participants with type 2 diabetes tested positive for Glutamic Acid Decarboxylase (GAD) autoantibodies [25], whilst a recently published study from the same group (Fremantle Diabetes Study 2) reported only 1/103 GAD positive and 6/102 IA-2 positive at a mean age of 55 years [26]. In the American GRADE study 3/14 of First Nations people tested positive for at least one autoantibody [22]. The rates and clinical associations of islet cell autoimmunity in NT First Nations peoples with diabetes or prediabetes, are not known.

This study aimed to assess islet autoimmunity to strengthen the understanding of its role in diabetes heterogeneity in younger First Nations women with diabetes to better inform management and outcomes.

2. Methods

2.1. Study context

Participants were recruited from the Northern Territory of Australia, where less than 250,000 people live in a 1.42 million square kilometres geographical area. First Nations peoples constitute approximately 26 % of the total population, with many residing in very remote communities [27]. Remoteness is a marker for absolute and relative social deprivation and is where the gap in morbidity and mortality between First Nations peoples and other Australians is at its most acute [28].

2.2. Participants

The Pregnancy and Neonatal Diabetes Outcomes in Remote Australia (PANDORA) cohort is an NT prospective observational birth cohort study of 1139 women with and without hyperglycaemia in their index pregnancy and their offspring. PANDORA was established to identify the factors contributing to intergenerational diabetes, with 46 % of the cohort identifying as First Nations women. The PANDORA study design has previously been published [29,30]. Follow-up of PANDORA participants after the index pregnancy was undertaken at Wave 1 (median: 2.1 years postpartum; range: 0.75 to 5.9 years) [16] and Wave 2 (median: 6.5 years postpartum; range: 6.8 to 11.1 years). This PANDORA sub-study included women from Wave 1 and Wave 2 who had consented to serum storage and met the inclusion criteria outlined below. Participants self-identified as First Nations women.

2.3. Inclusion criteria and definition of glycaemic groups

This PANDORA sub-study included 180 First Nations women (see Supplementary Fig. S1 for participant flow diagram). PANDORA participants were included if they met the criteria of one of the two glycaemic groups: (i) diabetes, which included women with a pregestational diagnosis of type 2 diabetes at the index pregnancy as self-described or from medical records or, when measured at Wave 1 or Wave 2, had a $HbA_{1c} \geq 6.5$ % (48 mmol/mol), or (ii) prediabetes HbA_{1c} 5.7 % – 6.4 % (39–47 mmol/mol) [31] at Wave 1 or Wave 2 with no previous reported diagnosis of diabetes at the index pregnancy. Women who were more than 6 weeks gestation in a subsequent pregnancy at review were excluded from this analysis.

2.4. Data measurements

Follow-up data collection occurred across the major towns and remote communities in the NT. Surveys, clinical, and anthropometric measures were collected by trained research staff using standardised methods. This included height, weight, waist and hip measurements, and blood pressure which were completed at the same time as the biological samples were sourced. Non-fasting blood samples (whole blood and serum) were collected for Wave 1, and fasting samples were collected after an overnight fast (> 8 h) for Wave 2. Random spot urine samples were collected at Wave 1 and Wave 2, and all blood and urine samples were stored at −80 degrees Celsius. HOMA modelling was not undertaken due to the low number of fasting participants in the sub-study cohort.

2.5. Laboratory methods

Testing for islet autoantibodies on stored serum was undertaken by the Royal Melbourne Hospital Endocrine Laboratory, which participates in the International Diabetes Autoantibody Standardization Program (IASP) [32]. Initial screening for any of the GAD, Insulinoma-Associated-2 (IA2) and Zinc Transporter-8 (ZnT8) autoantibodies was performed using the ELISA RSR^{TM} 3Screen Islet Cell Autoantibody (3Screen) test [33]. The sensitivity (Sn) and specificity of 3Screen were both 98 % for discriminating cases and controls in IASP 2024 (18/08/2025, oral communication, JMW, Royal Melbourne Hospital). Positive 3Screen tests were then tested by individual ELISA RSR^{TM} assays for GAD antibody (Sn 82 %), IA-2 antibody (Sn 74 %) and ZnT8 antibody (Sn 70 %). Positive thresholds for 3Screen, GAD, IA-2 and ZnT8 were ≥ 20 u/ml, ≥ 5 u/ml, ≥ 7.5 u/ml and ≥ 15 u/ml, respectively. Other clinical chemistry measures were performed by Monash Health Pathology in Melbourne. Lipid fractions, C-reactive peptide (CRP), urinary albumin and creatinine were measured using the Beckman Coulter AU5800 analyser. Glycated haemoglobin (HbA_{1c}) was measured in Wave 1 by cation-exchange high-performance liquid chromatography on the Arkray ADAMS^{TM} HA-8160 analyser and in Wave 2 using capillary electrophoresis on the Sebia CAPILLARYS 3 OCTA^{TM} analyser. C-peptide was measured using the Diasorin Liaison® XL Immunoassay analyser. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology) 2021 equation.

2.6. Statistical methods

Participant characteristics for each glycaemic group are presented as *n* (%), mean ± standard deviation or median [25th percentile (p25), 75th percentile (p75)] as appropriate. Hypertension is reported as a composite measure of either systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or participant reported prescribed antihypertensive medication. Triglyceride and high-density lipoprotein (HDL) are reported as median, p25, p75 and a composite categorical measure of dyslipidaemia including one or more of triglycerides ≥ 1.7 mmol/L, HDL < 1.3 mmol/L or participant reported lipid lowering medication. Renal measures are reported as eGFR in ml/min/1.73 m^2 as median, p25, p75 and categorical measures of eGFR < 60 ml/min/1.73 m^2 for stage 3 chronic kidney disease or > 125 ml/min/1.73 m^2 for glomerular hyperfiltration. Albuminuria is reported as microalbuminuria 3.5–34 mmol/mol or macroalbuminuria ≥ 35 mmol/mol. A composite variable of renal risk was defined as microalbuminuria, macroalbuminuria or eGFR < 60 ml/min/1.73 m^2.

Islet autoantibody positivity is reported across the glycaemic categories of prediabetes and type 2 diabetes as percentages of 3Screen positive, and individual autoantibody (IAb) positive (defined as any of GAD, IA-2 or ZnT8) and specific autoantibody positive for GAD, IA-2 or ZnT8 for all participants. Autoantibody titres are reported as units per millilitre and the C-peptide glucose ratio calculated [34]. Scatter graphs and calculation of Spearman's coefficient are performed for GAD and ZnT8 positive titres. Women with prediabetes and type 2 diabetes were separately compared by individual antibody positivity with regard to anthropometric measures, hypertension, C-peptide, C reactive peptide (CRP), lipid indices and albuminuria using the Fischer's exact test for categorical data, Student's *t*-test for continuous parametric data and the Mann Whitney *U* test for continuous non-parametric data. For women with diabetes, age at diabetes diagnosis, duration of diabetes, glycaemic measures and insulin use were also included. Statistical significance was considered as $p < 0.05$. All analyses were performed in Stata (v18, StataCorp, Texas).

2.7. Ethics and Governance

This study was approved by the Human Research Ethics Committee of the NT Department of Health and Menzies School of Health Research (NTHREC 10–1487, 15–2425 and 19–3431). Oversight was provided by the Aboriginal and Torres Strait Islander Advisory Group of the Diabetes Across the Lifecourse: Northern Australia Partnership.

3. Results

Among the 180 women in this analysis, there were 51 (28 %) women with prediabetes and 129 (72 %) with type 2 diabetes. The mean age at type 2 diabetes diagnosis was 30 years, and the median duration of diabetes at the time of assessment was 7 years (0–10.7 years). The majority of women with type 2 diabetes and prediabetes lived in very remote communities (71 %). The participant characteristics are noted in Table 1.

In women with prediabetes the frequency of a positive 3Screen test was 10/51 (19.6 %) and in women with type 2 diabetes 18/129 (13.9 %). In women with prediabetes the frequency of individual antibody positivity (any of GAD, IA-2 or ZnT8) was 5/51 (9.8 %) and in women with type 2 diabetes 11/129 (8.5 %) were positive. In women with prediabetes, 1/51 were positive for GAD and 4/51 for ZnT8. In women with type 2 diabetes 5/129 were positive for GAD, 1/129 for IA-2 and 6/129 for ZnT8. One woman with type 2 diabetes was positive for both GAD and ZnT8. Given the low numbers, statistical comparisons for GAD, IA-2 or ZnT8 positivity were not adequately powered. Individual antibody positivity is graphically represented in Fig. 1.

Table 2 outlines the clinical and metabolic characteristics according to positivity of any individual antibody (IAb) in participants with prediabetes and diabetes. There were no statistically significant differences between autoantibody positivity and age at diabetes diagnosis, diabetes duration, glycaemic indices or insulin use for women with type 2 diabetes, or C-peptide level, anthropometrics, renal and lipid indices, in those with prediabetes or diabetes. These comparisons are limited by the small numbers of participants positive for any individual autoantibody (n = 5 for prediabetes and n = 11 for diabetes).

Among the five women with type 2 diabetes who were positive for GAD autoantibodies (threshold > 5 u/ml), titres were 31, 133, 205 and > 2000 u/ml for two women. One woman with prediabetes had a GAD titre of 20 u/ml. Titres of ZnT8 autoantibody (threshold > 15 u/ml) were between 24–131 u/ml for the six women with diabetes and between 40 and 62 u/ml for the four women with prediabetes. Neither GAD nor

Table 1
Participant characteristics.

	n	Total	Prediabetes	T2D
n (%)		180 (100)	51 (28)	129 (72)
Age at diabetes diagnosis, years (SD)[a]	129	30.1 (7.6)	na	30.1 (7.6)
Duration diabetes diagnosis, years[a]	129	7.0 [0, 10.7]	na	7.0 [0.10.7]
Location [b]				
Regional *n* (%)	180	20 (11.1)	6 (11.8)	14 (10.9)
Remote, *n* (%)		33 (18.3)	7 (13.7)	26 (20.1)
Very remote, *n* (%)		127 (71.0)	38 (74.5)	89 (69.0)
HbA_{1c} NGSP, %	180	7.6 [6, 10.2]	5.9 [5.7, 6.0]	9.2 [7.3, 11.1]
HbA_{1c} IFCC, mmol/mol		59 [42, 87]	41 [39,42]	77 [56, 98]
BMI, kg/m2	176	29.8 [26.3, 34.2]	32.1 [27.6, 36.4]	29.1 [25.9, 33.4]
BMI ≥ 30 kg/m^2, *n* (%)	176	86 (49)	29 (60)	57 (45)
Waist / Hip Ratio (SD)	176	0.99 (0.09)	0.95 (0.97)	1.01 (0.08)
Hypertension composite, *n* (%)[c]	157	4 8 (31)	3 (8)	45 (38)
Triglycerides, mmol/L	179	2.0 [1.5, 3.0]	1.6 [1.3, 2.3]	2.2 [1.6, 3.1]
HDL-C, mmol/L	179	1.0 [0.8, 1.1]	0.9 [0.8, 1.1]	1.0 [0.8, 1.1]
Dyslipidaemia composite, *n* (%)[d]	179	168 (94)	46 (92)	122 (95)
eGFR, ml/min/1.73 m^2	179	116 [107, 122]	115 [102, 123]	116 [107, 121]
eGFR < 60, ml/min/1.73 m^2, *n* (%)	179	8 (4.5)	0	8 (6.2)
eGFR ≥ 125,ml/min/1.73 m^2, *n* (%)	179	25 (14)	11 (22)	14 (11)
Microalbuminuria, *n* (%)	158	56 (35)	11 (25)	45 (39)
Macroalbuminuria, *n* (%)	158	20 (13)	2 (5)	18 (16)
Renal risk composite[e], *n* (%)	179	81 (45)	13 (26)	68 (53)

Data collected at the same time as blood for antibody testing. Data are shown as n (%), mean (SD), or median [p25, p75].
BMI – Body Mass Index; eGFR- estimated glomular filtration rate; HDL-C – High Density Lipoprotein Cholesterol; IFCC – International Federation of Clinical Chemistry; NGSP – National Glycohemoglobin Standardization Programme; T2D – type 2 diabetes.
Legend:
a. Age at diagnosis and duration of type 2 diabetes. **b.** Modified Monash Categories.
c. Hypertension composite – SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or participant reported antihypertensive medication
d. Dysipidaemia composite – TG ≥ 1.7 mmol/L or HDL < 1.3 mmol/L or participant reported lipid lowering medication
e. Renal risk composite – Micro or macroalbuminuria or eGFR < 60 mls/min/1.73 m^2.
Missing data: Prediabetes/T2D: BMI n = 2/2; WHR n = 2/2; HTN n = 12/11; TG, HDL, eGFR, renal risk n = 1/0; ACR n = 7/15.

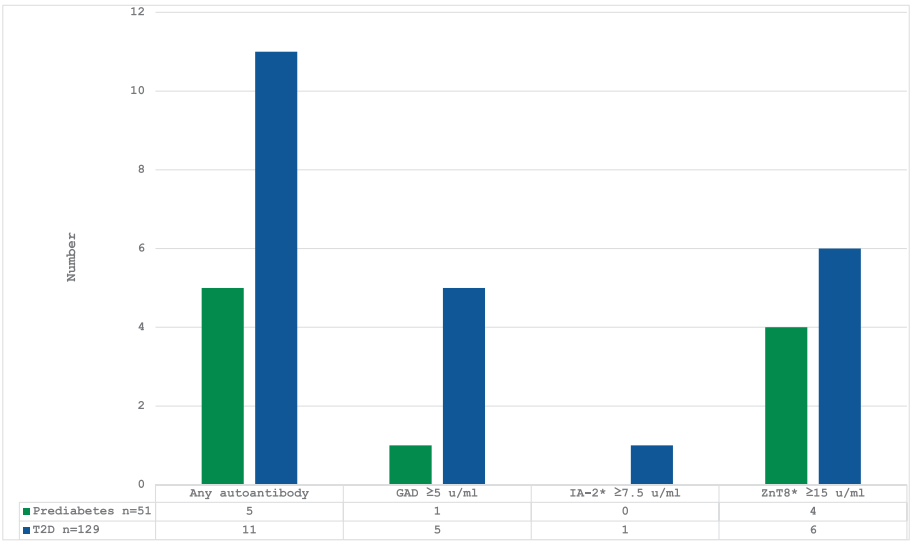

Fig. 1. Numbers of women with prediabetes and diabetes positive for islet cell autoantibodies.
Abbreviations: GAD - Glutamic Acid Decarboxylase autoantibodies; IA-2 - Insulinoma-Associated-2 autoantibodies; T2D - Type 2 Diabetes; ZnT8 - Zinc Transporter 8 autoantibodies

Table 2
Positive and negative autoantibody positivity in women with prediabetes and diabetes.

	n	Prediabetes IAb positive	Prediabetes IAb negative	*p*	n	Type 2 diabetes IAb positive	Type 2 diabetes IAb negative	*p*
n (%)	**51**	**5 (9.8)**	**46 (90.2)**		**129**	**11 (8.5)**	**118 (91.5)**	
Age at assessment, yrs (SD)	51	30 (7.8)	33 (6.5)	0.36	129	39.2 (4.9)	36.4 (5.8)	0.13
Age at T2D diagnosis, yrs (SD)					129	33.7 (5.2)	29.8 (7.7)	0.09
Duration T2D diabetes, yrs					129	3.2 [0, 16.5]	7.6 [0, 24.3]	0.70
BMI, kg/m^2	48	31.0 [25.8, 33.9]	32.0 [15.0, 58.0]	0.63	128	31.3 [19.2, 40.5]	28.9 [16.9, 51.6]	0.30
Waist-Hip Ratio	49	0.93 [0.89, 0.94]	0.98 [0.68, 1.17]	0.26	127	1.03 [0.92, 1.12]	1.01 [0.79, 1.20]	0.46
Hypertension composite *n* (%)[a]	39	0	3 (8)	0.60	118	4 (44)	41 (38)	0.68
HbA1c NGSP %						7.7	9.3	
					129	[6.5, 12.4]	[4.9, 16.7]	0.51
HbA1c IFCC mmol/mol						61 [48, 112]	78 [30, 159]	
C-Peptide, nmol/L[b]	51	1.56 [0.48, 5.91]	2.33 [0.48, 6.5]	0.86	129	2.31 [1.15, 5.29]	2.02 [0.16, 5.17]	0.18
HDL-C, mmol/L	50	0.84 [0.72, 1.22]	0.95 [0.66, 1.46]	0.20	129	0.83 [0.68, 1.09]	0.96 [0.42, 2.08]	0.05
Triglycerides, mmol/L	50	1.14 [0.74, 3.70]	1.72 [0.66, 4.60]	0.20	129	2.20 [1.0, 10.8]	2.20 [0.5, 8.8]	0.84
CRP, mmol/L	51	8.3 [3.9, 13.2]	8.6 [0.9, 33.9]	0.61	129	7.5 [2.5, 30.2]	8.3 [0.6, 184.7]	0.87
uACR > 3.5 mmol/mol *n* (%)	44	1 (20)	12 (31)	1.0	114	5 (50)	58 (56)	0.75
Insulin use *n* (%)					96	1 (13)	23 (26)	0.68

Data are shown as n (%), mean (SD), and median [p25, p75]. Significance testing with Fischer's exact, Student's *t*-test and Mann Whitney *U* test.
Abbreviations: IAb – any autoantibody positive of GAD, IA-2 or ZnT8; uACR – Urinary albumin creatinine ratio; CRP – C-reactive peptide; IFCC – International Federation of Clinical Chemistry; NGSP – National Glycohemoglobin Standardization Programme; T2D – type 2 diabetes.
a. BP ≥ 140/90 mmHg or prescribed medication **b.** random c-peptide normal range 0.26–1.39 nmol/L.
Missing data type 2 diabetes: IAb+/IAb-: BMI 1/0; WHR 0/2; HTN 2/9; HbA1c 0/1; ACR 1/14; Insulin use 3/30.
Missing data prediabetes: IAb+/IAb-: BMI1/2; WHR 1/1; HTN 2/10; HDL & TG 0/1; ACR 0/7.

ZnT8 titre were associated with C-peptide level or C-peptide:glucose ratio (see Supplementary Table 1 for details on individual women's titres and c-peptide indices, and Fig. S2 for scatter graphs and spearman's coefficient).

4. Discussion

This PANDORA sub-study investigating islet autoantibody positivity in younger First Nations women with prediabetes and type 2 diabetes yielded several findings. Firstly, 5/51 (10 %) of women with prediabetes and 11/129 (9 %) with diabetes tested positive for any individual autoantibody. Secondly, the most common autoantibody detected was

ZnT8 with 4/51 women with prediabetes and 6/129 women with diabetes testing positive. GAD autoantibody was positive in 1/51 woman with prediabetes and 5/129 women with diabetes. Thirdly, no statistically significant associations between individual autoantibody positivity were detected with random C-peptide, anthropometric measures, renal indices, or other cardiometabolic markers.

The frequency of GAD and IA-2 autoantibody positivity in First Nations women with type 2 diabetes in our study was 5/129 and 1/129, respectively. In comparison, the Australian urban Fremantle Diabetes Study 2 reported 1/103 for GAD, using the same assay, and 6/102 for IA-2 autoantibody positivity [26]. It reported no significant associations between IA and 2 positivity and either C-peptide, or age at diabetes diagnosis. However, the study did report that IA-2 positive participants had a longer duration of diabetes than those who were not positive. In PANDORA women with type 2 diabetes, 8.5 % tested positive for at least one of the individual autoantibodies, in comparison with the GRADE study which reported a frequency of 21 % though with substantially smaller numbers (3/14) [22]. Comparisons of autoantibody positivity between GRADE and PANDORA are limited by variability in antibody measurement and testing methods, non-reporting of antibody titres in GRADE, very small sample sizes, and differing population characteristics.

The significance of the ZnT8 positivity rate is not known. It was the most frequent positive individual antibody tested in this PANDORA sub-study with 4/51 women with prediabetes and 6/129 women with diabetes testing positive. This is higher than that reported in the Fremantle Diabetes Study 2 where none of the 103 First Nations participants tested positive utilising the same assay [26]. Recent findings from an Australian birth-cohort study that screened infants with a first-degree relative with type 1 diabetes using the same assays as our study, question the clinical relevance of a single ZnT8 autoantibody detected after age 4 years because it did not confer increased risk of progression to type 1 diabetes [35]. Studies from China, Iran and Argentina report 1 %, 3.4 % and 10.7 % positive rates in people with type 2 diabetes, respectively [36–38]. These three studies argued that ZnT8 was useful in discriminating Latent Autoimmune Diabetes in Adults (LADA) from type 2 diabetes in those who are GAD negative. This was not the case in PANDORA. In a retrospective cross-sectional study of an Estonian type 2 diabetes cohort, ZnT8 positivity was independently associated with the development of nephropathy [39]. This finding is of interest given the high prevalence of chronic kidney disease and kidney failure in First Nations women in the NT after a pregnancy complicated by GDM or pre-existing type 2 diabetes [40]. In the context of women at high risk of progression to type 2 diabetes, an Australian study of a GDM cohort of 302 women reported ZnT8 as the most prevalent autoantibody detected during pregnancy. The assay utilised was the same one used in PANDORA (RSR ELISA). In that GDM study, ZnT8A positivity was only associated with slightly elevated gestational fasting blood glucose levels and no other clinical correlates, and in five of the six women, ZnT8 was undetectable post-partum, suggesting minimal clinical significance in that population [41].

The lack of associations between GAD positivity and markers of beta cell function, anthropometrics and other metabolic markers in this PANDORA sub-study is in contrast to larger studies in populations with type 2 diabetes that generally report that islet autoimmunity is associated with lower measures of beta cell function and lower BMI [18,21,42,43]. A Chinese study of 1383 people with type 2 diabetes utilised the same screening assay and reported that 3Screen-positive individuals were statistically more likely to have a lower fasting C-peptide, fasting insulin, HOMA2-B and lower BMI and a higher HbA_{1c} as compared with 3Screen-negative participants [38]. The Fremantle Diabetes Study reported that the presence of GAD autoantibody in people diagnosed with type 2 diabetes was associated with lower BMI and waist circumference, lower triglycerides, higher HbA_{1c} and higher insulin use. However the GRADE study reported similar findings to PANDORA with no observed associations with anthropometrics or beta cell function [22]. The authors attributed this to small numbers, single autoantibody positivity and lower titres. In contrast, the GRADE study did report that T-cell-mediated autoimmunity was associated with lower beta cell function and higher glycaemia [22]. Both the Fremantle Diabetes Study and GRADE had a small number of GAD positive First Nations peoples within their cohorts.

The onset and course of autoimmune diabetes in adults is different to that of childhood type 1 diabetes. In adults, GAD has been reported as the dominant autoantibody, irrespective of the need for insulin treatment and has been consistent across multiple ethnicities, including those with low rates of HLA DR3, as found in some Asian populations [44]. Multiple autoantibody positivity is less likely with increasing age of onset and there is a lower risk of progression to clinical type 1 diabetes, with some individuals losing autoantibody positivity over time. Further, C-peptide levels are higher at diagnosis, and the rate of decline is inversely related to the age of onset [44]. A systematic review from 2015 reported the most discriminant clinical features, and suggest that adult-onset autoimmune diabetes is characterised by age at diagnosis (less than 40 years), low BMI (< 25 kg/m^2) and rapid need for insulin therapy [45]. Age of diabetes onset, as a risk for autoimmune diabetes, has become a less helpful marker in the context of an epidemic of type 2 diabetes in First Nations youth and younger adults. The median age of type 2 diabetes onset in our cohort was 29 years. A low BMI is also becoming a less discriminant marker of autoimmune diabetes. In the Look AHEAD study, the prevalence of autoantibody positivity was 12.8 % in the subgroup of type 2 diabetes participants with a BMI > 40 kg/m^2 [19]. The median BMI in each glycaemic group of our cohort was > 25 kg/m^2. Further, given differences in fat distribution in First Nations peoples of the NT, the healthy BMI range is considered lower than that for European populations [46].

While the comparisons of islet autoantibody frequency between different studies are interesting, there are limitations in these comparisons over time and across populations due to the variability in islet antibody measuring techniques, only fairly recent standardisation, the number of antibodies tested, and the lack of reporting of antibody titre in many studies. Much of this reflects the rapid evolution of knowledge in this area. Ethnicity may account for some of the differences in autoantibody prevalence across populations [1,25], but study comparisons are limited by inconsistent, poorly defined, reporting of “race”, “ancestry”, and “ethnicity” with the assumptions of genetic or socio-cultural differences that may or may not have some import to the study variables [47].

This study represents the highest number of First Nations peoples to date enrolled in an islet autoantibody study. A strength of this study is its enrolment of younger women with prediabetes and type 2 diabetes which is novel and different to the Fremantle Diabetes Study 2 that comprised an older group of men and women with type 2 diabetes alone. However, our findings on the association between individual antibody positivity and cardiometabolic characteristics are limited by the low numbers of autoantibody positivity. This impacts study power and statistical significance. There was also a suboptimal number of fasting participants, which limited information that HOMA modelling may have added in terms of beta cell function and insulin resistance. The small numbers in this PANDORA sub-study reflect the small, geographically sparse population of the NT, especially very remote living First Nations peoples, which also adds practical complexity to the feasibility of face-to-face research in this setting. The cross-sectional nature of this sub-analysis of PANDORA limits the understanding of islet autoimmunity over time in terms of the development of insulin deficiency in those with diabetes and progression to overt diabetes for those with prediabetes. The longitudinal nature of the PANDORA study will provide opportunities to further these observations going forward, and to further assess emerging complication profiles, especially in regard to the development of diabetic kidney disease. Given the PANDORA cohort includes a prospective cohort of women from their index pregnancy, it necessarily involves relatively young women, which limits generalisability to men

and, outside of remote Australia, to the general population.

A positive islet autoantibody test does not hold the promise of a simple diagnosis of autoimmune diabetes as these biomarkers can be positive in the wider general population [48]. The sensitivity and specificity of the test and the population prevalence of autoimmune diabetes are critical considerations when assessing positive autoantibody results in phenotypically type 2 diabetes patients. The 3Screen ELISA test utilised for screening in this study was highly sensitive [49] thus ensuring good capture of potential cases of autoimmunity but invariably including false positives. Specifically, in remote First Nations people with diabetes in the NT who currently have a very low prevalence of type 1 diabetes [12], single autoantibody positivity of low to medium titre more likely represents a 'biological false-positive' [48] and not autoimmune diabetes. This underlines the necessity of utilising specific measures, such as C-peptide, to assess insulin deficiency and guide management decisions.

In summary, to our knowledge, this PANDORA sub-study is the first to assess islet autoimmunity in a younger First Nations cohort of women with prediabetes and type 2 diabetes. This adds to the dearth of knowledge of islet autoimmunity in First Nations peoples. This study reports the frequency of individual islet cell autoantibody positivity of less than 10 % in women with prediabetes and type 2 diabetes. No clinical associations typical of type 1 diabetes were associated with Islet autoantibody positivity nor a distinct type 2 diabetes phenotype in younger First Nations women of the NT. Longitudinal follow-up of women positive for islet autoimmunity is required to determine glycaemic trajectories and potential insulin deficiency to ensure that diabetes management is tailored appropriately.

Role of the funder in the study

Funding bodies had no role in the study design, analysis, interpretation, manuscript preparation or decision to submit the manuscript for publication.

CRediT authorship contribution statement

Mary M. Wicks: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anna J. Wood:** Writing – review & editing, Investigation. **Angela Titmuss:** Writing – review & editing, Investigation. **Jonathan E. Shaw:** Writing – review & editing, Methodology. **John M. Wentworth:** Writing – review & editing, Methodology. **Peter G. Colman:** Writing – review & editing. **Alex D.H. Brown:** Writing – review & editing. **Louise J. Maple-Brown:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Elizabeth L.M. Barr:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2025.112977.

Data availability

Data are available on request to the Diabetes across the Lifecourse Northern Australian Partnership Steering Committee. They are not available on an online repository.

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