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Intergenerational risk of preterm birth in First Nations Australians: a population-based cohort study from the Northern Territory, Australia

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Abstract

Background PTB increases the risk of health problems such as chronic renal disease and diabetes in later life and adverse impacts are inversely correlated with gestational age at birth. Rates of PTB in the Northern Territory (NT) of Australia are amongst the highest nationally and globally, with First Nations babies most affected. This study assessed the magnitude and potential drivers of intergenerational PTB recurrence in the NT.

Methods A retrospective intergenerational cohort study (1986–2017) was conducted amongst 5,366 mothers born singleton who had 9,571 singleton live births (7,673 First Nations, and 1,898 non-First Nations babies). Maternal and offspring PTB was categorised as early (< 34 weeks) and late (34–36 gestational weeks). Modified Poisson regression was used to estimate the relative risk (RR) of PTB associated with maternal PTB, adjusting for moderators such as receipt of antenatal care prior to the offspring PTB. Secondary analyses assessed the impact of additional adjustment for conditions with a familial component, or that PTB predisposes to, on the risk estimate. Mediation analysis assessed the degree of mediation of maternal-offspring PTB relationships by these conditions.

Results Overall, First Nations women born preterm (< 37 weeks) had an increased risk of delivering before 37 gestational weeks (aRR 1.28; 95%CI 1.08, 1.51). Women born preterm had a higher risk of delivering early (< 34 gestational weeks) but not late preterm (34–36 weeks): the risk of early offspring PTB was increased amongst women themselves born early preterm (aRR 1.95, 95%CI 1.17, 3.24) or late preterm (aRR 1.41, 95%CI 1.01, 1.97). Adjustment for pre-eclampsia, intrauterine growth restriction, and hypertensive renal disease attenuated the observed intergenerational PTB associations. Mediation analysis suggested these conditions may mediate up to 26% of the observed intergenerational PTB recurrence. Similar trends were observed when first-time mothers were considered only. Maternal PTB status was not associated with PTB amongst non-First Nations women.

Conclusions First Nations women born preterm have an increased risk of early PTB. This association is in part driven by pre-eclampsia and hypertensive renal disease. Routine inquiry of maternal birth status may be a useful tool to identify NT First Nations women who may benefit from preventative measures.

Keywords Preterm birth, Early preterm birth, Intergenerational, First Nations

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Background

Gestational age at birth predicts neonatal and child survival, and preterm birth (PTB, birth before 37 completed gestational weeks) is a key driver of neonatal and infant mortality globally [1]. Surviving children born preterm are at higher risk of adverse physical and neurodevelopmental health outcomes in childhood and later life, impacting on their ability to thrive socioeconomically [2, 3]. PTB is a syndrome with multiple, often intersecting, aetiologies [4, 5]. There is substantial variation in the incidence of PTB by region, ethnicity, and socioeconomic status [6, 7]. Globally, rates of PTB have remained static over the last decade [6], highlighting the need to develop further tools to enable better prevention [8]. These include enhanced identification of women at elevated risk of PTB, who may benefit from preventative measures.

Epidemiological research suggests that PTB has a familial component. Several observational studies have reported associations between female siblings and PTB, and between parental PTB status and PTB in the offspring, indicating a degree of intergenerational recurrence [9–13]. Whilst paternal birth status appears to have a limited effect on PTB risk [10, 14], both maternal PTB status and a female family history appear to be implicated [15, 16], suggesting a role for either imprinting or mitochondrial inheritance [16]. Notably, observational data suggests that the risk of offspring PTB increases with decreasing gestational age at mothers' own birth [15, 17].

Key factors that may contribute to the apparent intergenerational effects PTB include diabetes, hypertensive disorders of pregnancy and intrauterine growth restriction, all of which have a familial component [18–21]. However, non-genetic factors such as intergenerational impacts mediated by environmental or socio-economic conditions shared by mother and offspring or between female siblings may also be important [10, 22]. Studies further reported that intergenerational effects may be more pronounced amongst specific population groups, as observed in the United States [23]. The causes of this apparent disparity in intergenerational PTB risk are poorly understood but are likely driven by socio-economic inequalities and differential access to care [7, 23].

The Northern Territory (NT) reports some of the highest PTB rates in Australia [24]. Aboriginal and Torres Strait Islander women (herein respectfully referred to as First Nations) are most affected, experiencing double the risk of PTB compared to non-First Nations women [11, 24, 25]. Key predictors associated with PTB in this setting included diabetes in pregnancy and pre-eclampsia [18, 19]. Other risk factors for PTB include tobacco smoking, and indicators of socio-economic disadvantage such as rheumatic heart disease, the latter associated with a higher likelihood of iatrogenic PTB [26]. In a large-population based study from Western Australia, parental history of PTB was associated with offspring PTB (odds ratio [OR] 1.25, $p<0.001$) in analyses adjusting for area level disadvantage, parity, maternal age and ethnicity [11].

Historically, some clinicians practising in the NT evaluated a maternal history of PTB in their assessment of PTB risk (David Simon, personal communication), suggesting intergenerational effects were considered important. Maternal PTB status currently does not inform local practice but may be useful clinical tool to identify women who may benefit from enhanced surveillance and targeted preventative measures in a high-burden setting.

The present study aimed to determine the magnitude of and contributing factors underlying the association of maternal PTB with offspring PTB in First-Nations and non-First Nations Australians who themselves were born and later birthed in the NT.

Methods

Study design

A retrospective population-based intergenerational cohort study was conducted to assess (a) the association of maternal PTB with offspring PTB; and (b) contributing factors to intergenerational risk of PTB.

Study setting and population

The study considered women born singleton in the NT, Australia, (1986 to 2002) who gave birth to live singleton infants ≥23 completed gestational weeks in the NT (2001 to 2017). The NT's population encompasses approximately 230,000 inhabitants across 1.3 million square kilometres [27]. According to the 2022-23 NT Health annual report 80% of the NT population resides in the Top End, the northern half of the NT, with the majority residing in and around the city of Darwin [28]. The Royal Darwin Hospital is the NT's only tertiary referral hospital with a neonatal intensive care unit. First Nations Australians make up ~26% of the NT population, with two-thirds residing outside of urban and peri-urban Darwin [29]. Approximately 10% of babies born in the NT are born preterm, with First Nations women having twice the rate of PTB (16%) compared to non-First Nations women (7%) [25].

Data sources and linkage

Two datasets were used in this study. The first dataset was the NT Perinatal Data Registry, which was established in 1986 as a statutory collection of antenatal, maternal, and perinatal information for all births in the NT. We accessed data from the NT Perinatal Data Registry for the period from July 1986 to December 2017. The second dataset was the NT Hospital Admissions dataset,

which contains detailed information for all admissions to all public hospitals in the NT from 1992 onwards. We accessed data from NT Hospital Admissions dataset for the period from July 1996 to December 2017. We prepared the analysis dataset by linking NT Perinatal Data Registry dataset with the NT Hospital Admissions dataset. Births in the NT Perinatal Data Registry from July 2001 to December 2017 were linked back to births in the NT Perinatal Data Registry from July 1986 to June 2001, to enable an evaluation of the association of maternal PTB status and offspring PTB. We assessed for data completeness, missingness, multicollinearity and potential misclassification of exposure variables and made appropriate corrections prior to analysis [30].

Datasets were sourced from an extensive repository of linked administrative datasets maintained by the Child and Youth Development Research Partnership (CYDRP), a collaboration work between Menzies School of Health Research and seven NT Government agencies. Data held in the repository are routinely collected as part of the service delivery. The first stage data linkage process was carried out by the SA-NT DataLink using a probabilistic linkage method with a clerical review of uncertain matches [29]. The detailed data linkage process has been described and published elsewhere [30]. The final stage of linking de-identified data files and preparing a dataset for this analysis was done by the research team.

Outcome

The outcome measure in this study was offspring PTB. Offspring PTB was defined as preterm (< 37 gestational weeks), and compared to term birth (≥ 37 weeks). To permit exploration of possible dose-relationships of maternal birth status with PTB risk in the offspring [15, 17], we further conducted analyses using categories of early and late PTB. Early PTB was defined as a birth that occurred between the gestational age of 23 to 33 weeks inclusive, and late PTB as a birth that occurred between 34 and 36 weeks inclusive. Gestational age at birth was determined by earliest fetal biometry, or by last menstrual period if a dating ultrasound was not done.

Exposure

The exposure tested was maternal PTB. Maternal PTB was categorised using the same parameters applied to the outcome, offspring PTB.

Covariates

Covariates were identified from the existing evidence base with selection of factors that were considered especially relevant to the NT context and population. They include the following: (i) maternal age (five categories: 15–19: 20–24, 25–29, 30–34, 35–45), antenatal clinic attendance in first trimester, and sex of the child ('male' and 'female'); (ii) Maternal adversity-related admissions such as maternal mental health-related hospital admissions five years prior to and during pregnancy (categorised as hospitalised for mental health, substance misuse, and hospitalised for both conditions) and maternal hospital admissions for violence-related events five years prior to and during pregnancy (yes or no); (iii) Perinatal factors (yes or no) such as pre-existing maternal and current obstetric complications (diabetes, pre-eclampsia, renal disease), morbidity complications during pregnancy (anaemia, urinary tract infection), maternal behavioral factors (smoking and alcohol consumption during pregnancy), parity (0, 1, 2, >=3), fetal complications such as intrauterine growth restriction, recorded as 'yes' or 'no'; (iv) community factors i.e., administrative health district where the mothers lived (Darwin Urban, Darwin Rural, Katherine, East Arnhem, Barkly, Alice Springs Urban, and Alice Springs Rural); and calendar year. These data were derived from the NT Perinatal data register.

We identified maternal mental health-related hospital admissions and history of adversity-related admission (violence) from the NT Hospital Admissions dataset using the International Statistical Classification of Disease and Related Health Problems 9th revision (ICD-9 concordance with ICD-10) and 10th Revision (ICD-10) diagnosis codes, as applied by similar studies [30–32]. The data contained diagnoses coded using ICD-10, allowing up to 10 diagnoses for a single admission. Women were considered having been hospitalised for mental health-related conditions as indicated by ICD-10 codes (e.g., F10-F99) listed as primary or up to nine secondary diagnosis codes as yes or no [31–33]. For admissions related to violence, we used ICD-10 codes within the range of X85-Y09 to capture external causes of morbidity and mortality, specifically assault-related injuries.

Statistical analysis

We calculated incidence rates of categories of PTB across various population groups with 95% confidence intervals. We calculated the number and proportion of births with each risk factor and their univariate association with the outcome variable using the Chi-square test of independence, for Fisher's exact test.

First, we estimated crude relative risks (RR) of offspring PTB by maternal PTB status. We subsequently included moderators (factors affecting the direction or strength of the PTB-PTB relationship) in a modified Poisson regression analyses to calculate adjusted RRs [34]. Moderators associated with offspring PTB at $p < 0.2$ on univariable analysis were considered for inclusion in these multivariable models (Model 1). Models used robust standard

errors to allow for clustering of births in a single woman and of births that occurred in the same hospital.

We subsequently tested Model 2, which additionally adjusted for conditions reported to have a familial component - pre-eclampsia, intrauterine growth restriction, hypertensive renal disease, diabetes – to assess the impact of adjusting for these factors on the PTB-PTB risk estimates. These conditions may in part mediate intergenerational PTB recurrence as they have a hereditary component and their development may have been a longer term adverse effect of women's own PTB [18–21, 35].

Lastly, the potential mediation effect of these hereditary conditions, hypothesised to lie on the causal pathways linking maternal PTB and offspring PTB, was evaluated using a Logit model (Stata version 17.0) [36]. The mediation analysis was conducted by first estimating the direct association between the primary exposure and preterm birth in a baseline model adjusted for aforementioned moderators, not on the causal pathway. Mediating covariates were incorporated into Model 2 to assess changes in the strength and significance of the exposure-outcome relationship. This stepwise approach allowed permitted exploration of the extent to which the hypothesised mediators could account for the observed association.

Analyses were stratified by First Nations status, estimating risks of offspring PTB for First Nations and non-First Nations women, as the burden of PTB substantially differs between the two populations [25]. Analyses were further conducted for first-time mothers, i.e., women without a history of offspring PTB that could guide clinical management and preventative strategies. As per conditions set by NT Health, reporting of cells with count < 5 was suppressed.

Results

A total of 5,709 NT-born women gave birth to 10,467 infants during the study period (Fig. 1). Following the exclusion of women who were themselves born of multiple pregnancies or had missing data for gestational age at birth, and exclusion of multiple pregnancies, undocumented ethnicity, age at birth < 15 years, and gestational age < 23 weeks, a total of 5,366 women who had 9,571 births were retained in the analysis.

There were 7,673 births to First Nations women (77.7%) and 1,898 births to non-First Nations women (22.3%) (Table 1). First Nations women were twice as likely to birth preterm (13.4%) compared to non-First Nations women (5.8%) ($p < 0.001$). Most offspring PTBs were spontaneous, with ~20% of offspring PTBs being

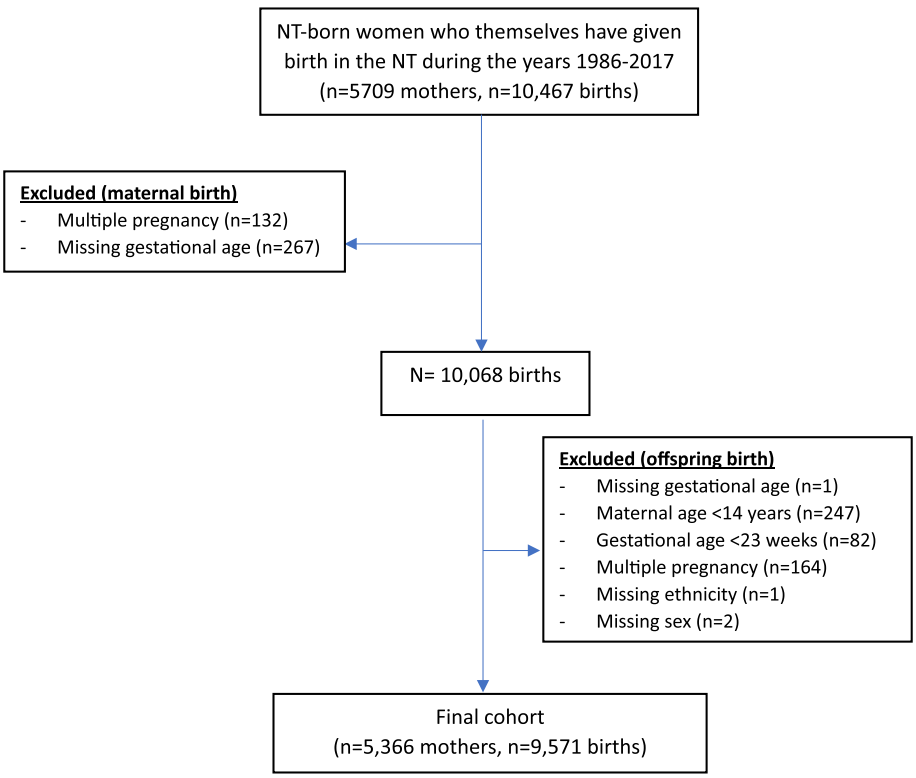

Fig. 1 Participant flow chart

Table 1 Incidence proportions of preterm birth (< 37 gestational weeks) in a retrospective intergenerational cohort from Northern Territory, Australia (1986 to 2017)

Population*	*N*	Incidence proportion, 95%CI
Overall population	1,137/9,571	11.9 (11.2, 12.5)
First Nations mothers	1,026/7,673	13.4 (12.6, 14.1)
Non-First Nations mothers	111/1,898	5.8 (4.8, 7.0)
Term births from term First Nations mothers	6,000/6,893	87.0 (86.2, 87.8)
Term births from term non-First Nations mothers	1,678/1,783	94.1 (92.9, 95.1)
Term births from preterm First Nations mothers	647/780	82.9 (80.1, 85.5)
Term births from preterm non-First Nations mothers	109/115	94.8 (89.0, 98.1)
Preterm birth from preterm mothers	139/895	15.5 (13.2, 18.1)
Preterm birth from term mothers	998/8,676	11.5 (10.8, 12.2)
Preterm birth from term First Nations mothers	893/6,893	12.9 (12.2, 13.8)
Preterm birth from term non-First Nations mothers	105/1,783	5.9 (4.8, 7.1)
Preterm birth from preterm First Nations mothers	133/780	17.1 (14.5, 19.9)
Preterm birth from preterm non-First Nations mothers	6/115	5.2 (1.9, 11.0)
Provider-initiated preterm birth	218/1,137	19.2 (16.9, 21.6)
Spontaneous preterm birth	919/1,137	80.8 (78.4, 83.1)
Preterm births that were provider-initiated amongst all preterm births to First Nations mothers	195/1,026	19.0 (9.6, 20.6)
Preterm births that were provider-initiated amongst all preterm births to non-First Nations mothers	23/111	20.7 (13.6, 29.4)

* The study population is offspring births

provider-initiated amongst both First Nations and non-First Nations' women (Table 1).

The incidence of PTB was higher amongst mothers with pre-existing diabetes mellitus, pre-eclampsia, intrauterine growth restriction, and smoking (Table 2). Additionally, amongst First Nations women, the incidence of PTB was higher amongst mothers with pre-existing hypertension with renal disease, a history of mental-health or violence-related hospital admission, alcohol consumption during pregnancy, and first antenatal clinic attendance after the first trimester. Urinary tract infection and teenage pregnancy were associated with a higher incidence of PTB amongst non-First Nations women. Sex of the baby, parity, gestational diabetes, and geographical location were not associated with PTB (Table 2).

Association of maternal preterm birth with offspring preterm birth amongst First Nations' women

Among First Nations' women who were themselves born preterm (maternal PTB), 17.0% of babies were born preterm, whilst among First Nations' women born term, 12.9% of babies were born preterm (Table 1).

Considering all preterm deliveries at any gestation (23–36 weeks), maternal PTB was associated with offspring PTB in both unadjusted analysis (RR 1.32; 95%CI 1.11, 1.55) and analysis adjusting for potential moderators (Model 1: aRR 1.28; 95%CI: 1.08, 1.51) such as anaemia, urinary tract infection, antenatal clinic attendance in first trimester, alcohol consumption, smoking during pregnancy, geographical area, mental health or violence-related hospitalisation, parity, and calendar year (Table 3). This association was substantially attenuated after additional adjustment for pre-eclampsia, hypertensive renal disease, intrauterine growth restriction and diabetes, i.e., hereditary or intergenerational conditions that could mediate the PTB-PTB relationship (aRR 1.18, 95%CI 1.00, 1.39) (Model 2, Table 3). Mediation analysis confirmed that pre-eclampsia, hypertensive renal disease, and intrauterine growth restriction partially mediate the association between being born preterm and delivering preterm, with a mediation effect of up to 26.0% (Table 4).

The impacts of early or late maternal PTB on early or late offspring PTB were then evaluated. Compared to women themselves born at term, women born early preterm (< 34 gestational weeks) had a twofold increase of early PTB on crude (RR: 2.30, 95%CI 1.36, 3.89) and adjusted analyses (Model 1: aRR 1.95; 95%CI 1.17, 3.24). As observed in analyses consider all PTBs, this association attenuated after additional adjustment for pre-eclampsia, intrauterine growth restriction, hypertensive renal disease and diabetes (Model 2: aRR 1.53, 95%CI 0.95, 2.58). Similarly, women themselves born late

Table 2 Maternal characteristics and the bivariable association with preterm birth in the Northern Territory, Australia (1986 to 2017)

	Preterm birth, % (n/n total)			
	First Nations	***p*-value**	**Non-First Nations**	***p*-value**
Mother born preterm		0.001		0.766
Yes	17.1 (133/780)		5.2 (6/115)	
No	12.9 (893/6,893)		5.9 (105/1,783)	
Sex		0.507		0.480
Male	13.6 (535/3,925)		6.2 (58/935)	
Female	13.1 (491/3,748)		5.5 (53/963)	
Parity		0.584		0.122
0	13.0 (507/3,900)		NR	
1	14.2 (318/2,239)		NR	
2	13.0 (134/1,030)		NR	
>=3	13.3 (67/504)		NR	
ANC in the first trimester		< 0.001		0.261
No	11.6 (413/3,559)		NR	
Yes	13.8 (545/3,949)		NR	
Missing	41.0 (68/165)		NR	
Pre-existing diabetes mellitus		< 0.001		0.042
No	13.2 (1,009/7,622)		NR	
Yes	33.3 (17/51)		NR	
Pre-existing hypertension with renal disease		< 0.001		0.575
No	13.1 (978/7,493)		NR	
Yes	26.7 (48/180)		NR	
Gestational diabetes		0.712		0.675
No	13.3 (942/7,069)		5.9 (106/1,796)	
Yes	13.9 (84/604)		4.9 (5/102)	
Pre-eclampsia		< 0.001		< 0.001
No	12.3 (900/7,299)		5.5 (100/1,832)	
Yes	33.7 (126/374)		16.7 (11/66)	
Anaemia		0.006		0.502
No	13.8 (919/6,662)		NR	
Yes	10.6 (107/1,011)		NR	
Intrauterine growth restriction		< 0.001		< 0.001
No	12.7 (920/7,256)		5.6 (103/1,840)	
Yes	25.4 (106/417)		18.2 (8/44)	
Complications of UTI		0.887		0.023
No	13.4 (948/7,099)		NR	
Yes	13.6 (78/574)		NR	
Teen motherhood		0.848		0.042
< 20 years	13.5 (437/3,237)		8.0 (31/388)	
>=20 years	13.3 (589/4,436)		5.3 (80/1,510)	
Alcohol consumption in pregnancy		< 0.001		0.026
No	10.7 (564/5,286)		NR	
Yes	15.4 (93/604)		NR	
Missing	20.7 (369/1,783)		NR	
Smoking in pregnancy		0.000		0.053
No	9.3 (82/882)		3.5 (7/205)	
Yes	11.4 (120/1,053)		9.9 (12/12)	
Missing	14.4 (824/5,738)		5.9 (92/1,559)	
History of mental-health related hospitalisation[a]		0.017		0.079

Table 2 (continued)

	Preterm birth, % (n/n total)			
	First Nations	***p*-value**	**Non-First Nations**	***p*-value**
No	13.3 (936/7,026)		NR	
Yes	17.2 (63/366)		NR	
Missing	9.6 (27/281)		NR	
History of violence-related hospitalisation		0.002		0.190
No	13.3 (938/7,071)		NR	
Yes	19.0 (61/321)		NR	
Missing	9.6 (27/281)		NR	
Epidemiological district		0.271		0.586
Darwin urban	10.6 (105/995)		NR	
Darwin rural	15.8 (245/1,556)		NR	
Katherine	12.9 (175/1,357)		NR	
East Arnhem	15.4 (172/1,120)		NR	
Barkly	13.2 (77/585)		NR	
Alice Spring urban	12.2 (72/592)		NR	
Alice Spring rural	12.5 (158/1,268)		NR	

Data are % (n/n total). NR, not reported as one or more cell counts < 5

[a] Defined as any mental health-related hospitalisation within five years prior to and during pregnancy

preterm (34–36 gestational weeks) were more likely to have an early PTB on crude (RR 1.41, 95%CI 1.02, 1.97) and adjusted analyses (Model 1: aRR 1.41, 95%CI 1.01, 1.97) compared to mothers born term; again, this association attenuated when further adjusted for aforementioned hereditary conditions (Model 2: aRR 1.35, 95%CI 0.97, 1.86).

In analyses considering first-time mothers only ($n = 3,903$), there were trends towards increased risk of early PTB amongst women who themselves were born early preterm (RR 2.24, 95%CI 1.08, 4.62; Model 1: aRR 1.98; 95%CI 0.99, 3.97) or born late preterm (RR 1.58, 95%CI 1.01, 2.47; Model 1: aRR 1.56, 95%CI 1.00, 2.43).

There was more limited evidence of an association between maternal PTB status and late PTB in the offspring: women, whether themselves born early or late preterm, did not have increased risks of late PTB compared to mothers born at term.

Association of maternal preterm birth with offspring preterm birth amongst non-First Nations' women

Amongst non-First Nations' women born preterm, 5.2% of babies were born preterm, whilst among non-First Nations' women born term, 5.9% of babies were born preterm (Table 1). Maternal PTB status did not associate with offspring PTB in this population on crude (RR 0.97, 95%CI 0.89, 1.07) and adjusted analyses (Model 1: aRR 0.87, 95%CI 0.39, 1.94). Table 3). There were too few observations to evaluate PTB-PTB relationships by early and late PTB (Table 3).

Discussion

First Nations women who themselves were born preterm have a 30% increased risk of PTB but maternal PTB status was not associated with offspring PTB in non-First Nations women. Intergenerational influence of PTB risk was highest amongst First Nations women who themselves were born early preterm. These women had double the risk of an early PTB, which is associated with profound adverse health effects, compared to women who were born at term. Similarly, First Nations women born themselves late preterm had a 40% increase in risk of early PTB. Similar trends were observed when analyses considered first-time mothers only. In analyses adjusting for hereditary conditions or conditions which a mother may be more likely to develop as a result of herself being born preterm, the association between maternal PTB status and offspring PTB attenuated, suggesting a degree of mediation of intergenerational PTB risk by these conditions. Mediation analysis indicated that ~25% of intergenerational PTB recurrence risk may be mediated by preeclampsia, hypertensive renal disease, and intrauterine growth restriction.

Limited progress has been made with reducing PTB rates in First Nations Australians [25, 37]. Rates of early PTB remain high, rates of late PTB have increased, and population disparities persist [25, 37]. Our findings align with findings from an intergenerational cohort study from Western Australia [11], indicating that disparities in PTB risk appear to transcend generations, with maternal PTB status being a stronger predictor of offspring PTB

Table 3 Association between maternal preterm birth status and preterm birth in the Northern Territory, Australia (1986 to 2017) – modified Poisson regression

	Preterm birth			
	First Nations babies (*n* = 7,673)		**Non-First Nations babies (1,898)**	
	cRR	**aRR**	**cRR**	**aRR**
Mother born preterm				
No	Ref	Ref	Ref	Ref
Yes[a]	1.32 (1.11, 1.55)*	1.28 (1.08, 1.51)*	0.97 (0.89, 1.07)	0.90 (0.41, 1.99)
Yes[b]	1.32 (1.11, 1.55)*	1.18 (1.00, 1.39)	0.97 (0.89, 1.07)	0.87 (0.39, 1.94)
Mother born preterm (first pregnancy)				
No	Ref	Ref	Ref	Ref
Yes[a]	1.10 (0.86, 1.41)	1.06 (0.83, 1.36)	0.25 (0.04, 1.79)	0.26 (0.04, 1.82)
Yes[b]	1.10 (0.86, 1.41)	0.95 (0.75, 1.22)	0.25 (0.04, 1.79)	0.28 (0.04, 1.98)
	Early preterm birth			
Mother born				
Term	Ref	Ref	N/A	N/A
Early preterm[a]	2.30 (1.36, 3.89)*	1.95 (1.17, 3.24)*	N/A	N/A
Late preterm[a]	1.41 (1.02, 1.97)*	1.41 (1.01, 1.97)*	N/A	N/A
Early preterm[b]	2.30 (1.36, 3.89)*	1.53 (0.91, 2.58)	N/A	N/A
Late preterm[b]	1.41 (1.02, 1.97)*	1.35 (0.97, 1.86)	N/A	N/A
Mother born (first pregnancy)				
Early preterm[a]	2.24 (1.08, 4.62)*	1.98 (0.99, 3.97)	N/A	N/A
Late preterm[a]	1.58 (1.01, 2.47)*	1.56 (1.00, 2.43)	N/A	N/A
Early preterm[b]	2.24 (1.08, 4.62)*	1.39 (0.69, 2.79)	N/A	N/A
Late preterm[b]	1.58 (1.01, 2.47)*	1.49 (0.97, 2.28)	N/A	N/A
	Late preterm birth			
Mothers born				
Term	Ref	Ref		
Early preterm[a]	1.59 (1.04, 2.43)*	1.41 (0.91, 2.17)	N/A	N/A
Late preterm[a]	1.16 (0.91, 1.48)	1.15 (0.90, 1.46)	N/A	N/A
Early preterm[b]	1.59 (1.04, 2.43)*	1.21 (0.77, 1.90)	N/A	N/A
Late preterm[b]	1.16 (0.91, 1.48)	1.10 (0.87, 1.40)	N/A	N/A
Mother born (first pregnancy)				
Early preterm[a]	1.12 (0.58, 2.17)	1.00 (0.51, 1.95)	N/A	N/A
Late preterm[a]	0.79 (0.53, 1.18)	0.79 (0.53, 1.17)	N/A	N/A
Early preterm[b]	1.12 (0.58, 2.17)	0.80 (0.40, 1.60)	N/A	N/A
Late preterm[b]	0.79 (0.53, 1.18)	0.76 (0.52, 1.12)	N/A	N/A

N/A not available

*$P < 0.05$

[a] Adjusted for anaemia, urinary tract infection, antenatal clinic attendance in first trimester, alcohol consumption, smoking during pregnancy, geographical area, mental health-related hospitalisation, violence five years before pregnancy, parity, and calendar year

[b] Model 2: Adjusted for all factors in Model 1 plus preeclampsia, pre-existing diabetes mellitus, gestational diabetes, hypertensive renal disease, and intrauterine growth restriction

amongst First Nations as compared to non-First Nations women. In our cohort, key factors influencing intergenerational risk of PTB in First Nations women included pre-eclampsia and pre-existing hypertensive renal disease. These factors have been reported to have a substantial familial component [38, 39]. Furthermore, PTB itself may increase the risk of early onset hypertensive renal disease, which is common amongst Australian First Nations peoples, thereby perpetuating the intergenerational risk of PTB in this population [40].

For parous women with a singleton pregnancy, a history of a previous PTB is one of the strongest predictors of PTB risk in a subsequent pregnancy and commonly used in clinical practice to guide implementation of

Table 4 Mediation analysis for association between being born preterm and having a preterm birth in First Nations women, Northern Territory, Australia

Exposure	Direct effect	Indirect effect	Total effect	Proportion of indirect effect
Born preterm-◊ IUGR-◊ having preterm	1.31 (1.05, 1.63)	1.03 (1.01, 1.05)	1.34 (1.08, 1.68)	8.7%
Born preterm-◊ Preeclampsia -◊ having preterm	1.29 (1.01, 1.59)	1.04 (1.01, 1.08)	1.34 (1.08, 1.67)	13.8%
Born preterm-◊ pre-existing hypertensive renal disease -◊ having preterm	1.31 (1.06, 1.63)	1.02 (0.99, 1.04)	1.34 (1.09, 1.65)	NA
Born preterm-◊ (Preeclampsia, IUGR, and pre-existing hypertensive renal disease)-◊ having preterm	1.24 (1.05, 1.46)	1.08 (1.03, 1.13)	1.34 (1.13, 1.59)	26.0%

IUGR Intrauterine growth restriction

preventative strategies [41, 42]. However, identifying nulliparous women at increased risk of PTB is more challenging. In our high burden setting, establishing maternal birth status amongst First Nations Australians may be a useful and potentially cost-effective tool to recognise women who may benefit from targeted preventative measures, as maternal PTB status can be determined through routine enquiry at antenatal booking. Enquiry of maternal birth status is particularly relevant for first time mothers, who aside from the now routine cervical length measurement at the 18–20 weeks morphology scan, are not specifically screened for PTB risk in our setting [43]. Screening for pre-eclampsia at antenatal booking may prove to be an important strategy to reduce some of the intergenerational PTB risk. History-based provision of low dose aspirin from 12 gestational weeks for prevention of pre-eclampsia is currently recommended by the National Institute of Health and Care Excellence in women with a family history and one other moderate risk factor, such as nulliparity, and among women with chronic kidney disease [44, 45] More advanced pre-eclampsia screening through an algorithm encompassing medical history, 12–14 week uterine artery dopplers, body mass index, and placental protein measurements, may also be helpful but likely faces significant implementation challenges in remote settings, where the majority of the NT First Nations women reside.

Additional preventative measures could be considered in nulliparous women born preterm. Determining the characteristics of maternal PTB may be key, in that women where were born themselves by spontaneous preterm birth in absence of, e.g., pre-eclampsia, may benefit from, e.g., vaginal progesterone and/or additional cervical length monitoring in their own first pregnancy, whereas women whose own preterm birth was likely driven by pre-eclampsia, or who have other risk factors for pre-eclampsia, may benefit more from low-dose aspirin. However, ascertainment of the circumstances of the maternal PTB may be challenging. Efforts to support smoking cessation amongst all women is likely to reduce PTB and other adverse pregnancy and maternal health outcomes [8], and may reduce the impact of PTB on the development of early-onset renal dysfunction in First Nations babies [40]. Larger population studies are required to consolidate the association between various phenotypes of PTB across generations, in order to determine the most suitable preventative measures that should be evaluated in clinical trials or implementation studies.

Our study has several limitations. First, we were unable to link female siblings of the mother to assess the relevance of female history of PTB in our setting, which may be of importance and could enhance our ability to identify women at elevated risk of PTB [15]. Furthermore, whilst reported of limited significance in other settings, we were unable to ascertain paternal birth status and its role in intergenerational PTB risk in the NT. Thirdly, we opted to retain all linkable singleton pregnancies in the model, including singleton pregnancies of multiparous women. Analyses were adjusted for parity and clustering (several pregnancies to a single women), but not for previous PTB. However, analyses considering first births indicated trends similar to those observed when all births were considered. Furthermore, there were too few non-First Nations women in the sample to conduct analyses stratifying by early and late preterm birth in this population. The relatively smaller number is consistent with the high level of interstate migration of the NT non-First Nations population and possibly a higher proportion of interstate births for amongst non-First Nations women, including transfers for women at risk of extreme preterm birth. Lastly, residual confounding of unknown or unmeasured confounders may account for some of the associations between maternal birth status and preterm birth in our cohort.

Conclusions

NT First Nations women born preterm themselves have an increased risk of PTB, in particular early PTB. This association was in part mediated by pre-eclampsia,

hypertensive renal disease and intrauterine growth restriction. Routine inquiry and record of First Nations women's own PTB status in the NT may be a useful tool to identify women at increased risk who may benefit from preventative measures to break the intergenerational cycle of PTB.

Abbreviations

aRR	Adjusted risk ratio
CI	Confidence interval
N/A	Not available
NR	Not reported
NT	Northern Territory
PTB	Preterm birth
RR	Risk ratio

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Authors' contributions
HWU, SG, and DS conceived the project and designed the study. AD and SG prepared the data. AD, HWU and SG analysed the data. HWU and AD drafted the first version of the manuscript. All authors participated in the interpretation of the data and revision of the manuscript. All authors read and approved the final manuscript.

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Data availability
The authors do not have permission to share patient-level data extracted from the NT Midwives perinatal data set or 'NT Midwives' Collection'. Data can only be made available to researchers who apply to the Human Research Ethic Committee of the Northern Territory Department of Health and Menzies School of Health Research (Ethics - Menzies) and the Child and Youth Development Research Partnership repository (Child and Youth Development Research Partnership CYDRP 2017-2024 - Menzies).

Declarations

Ethics approval and consent to participate
This project was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC – 2018-3261) and was supported by a First Nations Advisory Group, which includes independent First Nations community members.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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