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Hyperglycemia in pregnancy and developmental outcomes in children at 18–60 months of age: the PANDORA Wave 1 study

Angela Titmuss[1,2], Anita D'Aprano[3,4,5], Federica Barzi[1,6], Alex D.H. Brown[7,8], Anna Wood[1,9], Christine Connors[10], Jacqueline A. Boyle[1,11], Elizabeth Moore[12], Kerin O'Dea[8], Jeremy Oats[13], H. David McIntyre[14], Paul Zimmet[15], Jonathan E. Shaw[16], Maria E. Craig[17] and Louise J. Maple-Brown[1,9]

[1]Wellbeing and Preventable Chronic Diseases Division, Menzies School of Health Research, Charles Darwin University, Darwin, NT, Australia; [2]Paediatric Department, Division of Women, Children and Youth, Royal Darwin Hospital, Darwin, NT, Australia; [3]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia; [4]Murdoch Children's Research Institute, Melbourne, VIC, Australia; [5]Centre for Child Development and Education, Menzies School for Health Research, Charles Darwin University, Darwin, NT, Australia; [6]Poche Centre for Indigenous Health, University of Queensland, Brisbane, QLD, Australia; [7]Wardliparingga Aboriginal Research Unit, South Australian Health and Medical Research Institute, Adelaide, SA, Australia; [8]University of South Australia, Adelaide, SA, Australia; [9]Endocrinology Department, Division of Medicine, Royal Darwin Hospital, Darwin, NT, Australia; [10]Northern Territory Department of Health, Darwin, NT, Australia; [11]Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia; [12]Public Health Unit, Aboriginal Medical Services Alliance of Northern Territory, Darwin, NT, Australia; [13]Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia; [14]Faculty of Medicine, Mater Medical Research Institute, University of Queensland, Brisbane, QLD, Australia; [15]Department of Diabetes, Central Clinical School, Monash University, Melbourne, VIC, Australia; [16]Clinical and Population Health, Baker Heart and Diabetes Institute, Melbourne, VIC, Australia and [17]School of Women and Children's Health, University of New South Wales, Sydney, NSW, Australia

Abstract

This study aimed to explore the association between hyperglycemia in pregnancy (type 2 diabetes (T2D) and gestational diabetes mellitus (GDM)) and child developmental risk in Europid and Aboriginal women.

PANDORA is a longitudinal birth cohort recruited from a hyperglycemia in pregnancy register, and from normoglycemic women in antenatal clinics. The Wave 1 substudy included 308 children who completed developmental and behavioral screening between age 18 and 60 months. Developmental risk was assessed using the Ages and Stages Questionnaire (ASQ) or equivalent modified ASQ for use with Aboriginal children. Emotional and behavioral risk was assessed using the Strengths and Difficulties Questionnaire. Multivariable logistic regression was used to assess the association between developmental scores and explanatory variables, including maternal T2D in pregnancy or GDM.

After adjustment for ethnicity, maternal and child variables, and socioeconomic measures, maternal hyperglycemia was associated with increased developmental "concern" (defined as score ≥1 SD below mean) in the fine motor (T2D odds ratio (OR) 5.30, 95% CI 1.77–15.80; GDM OR 3.96, 95% CI 1.55–10.11) and problem-solving (T2D OR 2.71, 95% CI 1.05–6.98; GDM OR 2.54, 95% CI 1.17–5.54) domains, as well as increased "risk" (score ≥2 SD below mean) in at least one domain (T2D OR 5.33, 95% CI 1.85–15.39; GDM OR 4.86, 95% CI 1.95–12.10). Higher maternal education was associated with reduced concern in the problem-solving domain (OR 0.27, 95% CI 0.11–0.69) after adjustment for maternal hyperglycemia.

Maternal hyperglycemia is associated with increased developmental concern and may be a potential target for intervention so as to optimize developmental trajectories.

Original Article

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Address for correspondence:
Dr Angela Titmuss, Wellbeing and Preventable Chronic Diseases Division, Menzies School of Health Research, Charles Darwin University, PO Box 41096, Casuarina, NT, 0811, Australia.
Email: Angela.titmuss@menzies.edu.au

On behalf of the PANDORA Study research team.

Introduction

Early experiences are key to a child's developmental trajectory, through both cumulative risk factors over time, and biological programming of adversities during critical periods of developmental vulnerability.[1–3] *In utero* exposures such as hyperglycemia in pregnancy are also important[4] and timing of exposure is key.[5–8] Developmental trajectories are influenced by many factors, including child factors such as *in utero* exposures, health, age, and gender; family factors, such as engagement, educational attainment, employment, culture, trauma, and health; and the wider social environment.[9] Many factors need to positively align to promote optimal child developmental outcomes. Early childhood therefore represents a "critical window of opportunity"[10] for intervention and support to promote optimal child developmental outcomes.

Children born to mothers with hyperglycemia in pregnancy may have a higher risk of fine and gross motor difficulties, autism,[11] inattention and hyperactivity,[12] correlating with degree of maternal hyperglycemia.[13] However, evidence of the effect on the developing brain is conflicting, with some studies indicating no difference in developmental outcomes in children born to mothers with diabetes.[14,15] The ongoing impact of maternal type 2 diabetes (T2D), obesity, food security and nutrition post-birth on child development is also unknown. Limitations of previous studies include heterogeneity in design, retrospective determination of maternal diabetes status from medical records, difficulty ascertaining the effect of maternal obesity, confounders such as socioeconomic status (SES), and relatively small study size.[16]

The majority of previous studies have assessed gestational diabetes mellitus (GDM), with few examining the effect of T2D in pregnancy.[16] This is important as the metabolic changes in T2D are present from the pregestational period and in early pregnancy, possibly having a more severe impact on neurocognitive development. Exposure to hyperglycemia *in utero* may also be an additive risk to other vulnerabilities for childhood behavioral difficulties, such as low SES.[17] Socioeconomic status and ethnicity are themselves risk markers for maternal hyperglycemia in pregnancy, influencing a mother's access to health care, nutrition, food security, mental health, wellbeing, and likelihood of a health-promoting social environment.[9,18–20]

Assessment of the differential risk of exposure to T2D in pregnancy compared with GDM is a key current evidence gap. As a prospective follow-up of a birth cohort, the Pregnancy and Neonatal Diabetes Outcomes in Remote Australia (PANDORA) Wave 1 study is uniquely positioned to contribute to knowledge regarding the impact of exposure to T2D in pregnancy versus GDM due to a much higher proportion of women with T2D than other studies. The prospective nature also allows assessment of the influence of maternal BMI and socioeconomic vulnerabilities on developmental risk over time.

In the Australian setting, Aboriginal cultures have deep and long connections to country and language, enriching family structures and children's development. Aboriginal children, however, also face significant systemic inequities that may impact on their developmental trajectory, including socioeconomic vulnerability, inadequate housing, chronic medical conditions such as anemia and hearing impairment, higher risk of being placed in out of home care, intergenerational trauma, discrimination and loss, and exposure to domestic violence.[21] These factors are thought to contribute to significant health inequities,[22] and much higher prevalence of cardiometabolic conditions, including diabetes[9,18–20] PANDORA has a high proportion of Aboriginal women as participants, reflecting the 10-fold higher prevalence of T2D in pregnancy in Aboriginal women than non-Indigenous Australian women.[23]

The PANDORA Wave 1 study aimed to i) assess the association of maternal glycemic status in pregnancy with developmental vulnerability of children and ii) explore how this association is influenced by socioeconomic status. This study can provide important information for Aboriginal communities and inform strategies to optimize developmental trajectories.

Methods

Participants

PANDORA Wave 1 is an early childhood substudy of a longitudinal birth cohort, involving 1139 women and 1169 children across the Northern Territory (NT), Australia.[24] Women aged 16 years and over with T2D or GDM were recruited from the NT Diabetes in Pregnancy Register, and women with normoglycemia from antenatal clinics between November 2011 and February 2017. Diagnostic criteria for GDM and the recruitment process have previously been described.[25] Measures of severity of hyperglycemia differ between categories of maternal glycemia, with oral glucose tolerance test results available for women with GDM, and glycated hemoglobin in women with T2D.

Eligible children for PANDORA Wave 1 (Fig. 1) were from five groups, classified by maternal glycemic status and ethnicity. Women with type 1 diabetes ($n = 16$) and Europid women with T2D ($n = 9$) were excluded due to small numbers, noting that T2D is uncommon in pregnant Europid women across Australia. Women of other ethnicities (non-Europid, non-Aboriginal) were excluded. There are 900 women with either T2D or GDM within PANDORA (54% of all women on register),[25] of whom 638 were eligible to participate in Wave 1, and 222 women with normoglycemia, all of whom were eligible (as by design this group included only Aboriginal or Europid women). Wave 1 was completed in December 2018 and involved 416 mothers and 423 children (255 Aboriginal and 168 Europid) aged 18–60 months.

Mother and child characteristics

Antenatally and at Wave 1 study visit, mothers completed questionnaires regarding demography, medical history, and child health.[25] Body mass index at first antenatal visit (kg/m^2) used weight and height recorded at first antenatal visit and was adjusted for gestational age at time of first antenatal visit. Smoking in pregnancy was self-reported (during pregnancy and immediately after birth), categorized as yes/no. Self-reported measures of socioeconomic status included educational attainment (categorized within this study as completion of ≤10 years vs >10 years of schooling), employment (employed vs unemployed/not seeking employment), source of income (wage/salary vs welfare payment/student payment) and home ownership (owner occupier vs rent or other tenure). Remote residence was determined using maternal home address, categorized as either living within the three urban centers of the NT or in other areas.

Prematurity was defined as gestational age at birth less than 37 weeks, categorized as yes/no. Child age was determined as of date of Wave 1 study visit. Child BMI (kg/m^2) was calculated using weight and height measured at time of Wave 1 visit.

Developmental screening tools

Children underwent developmental screening, administered through interview, using either an age-appropriate Ages and Stages Questionnaire®, Third Edition (ASQ®-3), or a culturally adapted ASQ for Aboriginal children (Talking about Raising Aboriginal Kids ASQ-TRAK),[26] exploring gross motor, fine motor, communication, personal-social and problem-solving developmental domains.[27–29] Screening was undertaken once, at the time of Wave 1 study visit (conducted when the child was between 18 and 60 months of age).

ASQ-3

ASQ-3 was used for all Europid children, or Aboriginal children living in urban areas, with English as a first language, who were of ages where ASQ-TRAK is not validated (see below). ASQ-3 was available for 18-, 20-, 22-, 24-, 27-, 30-, 33-, 36-, 42-, 48-, 54-, and 60-month-old children.

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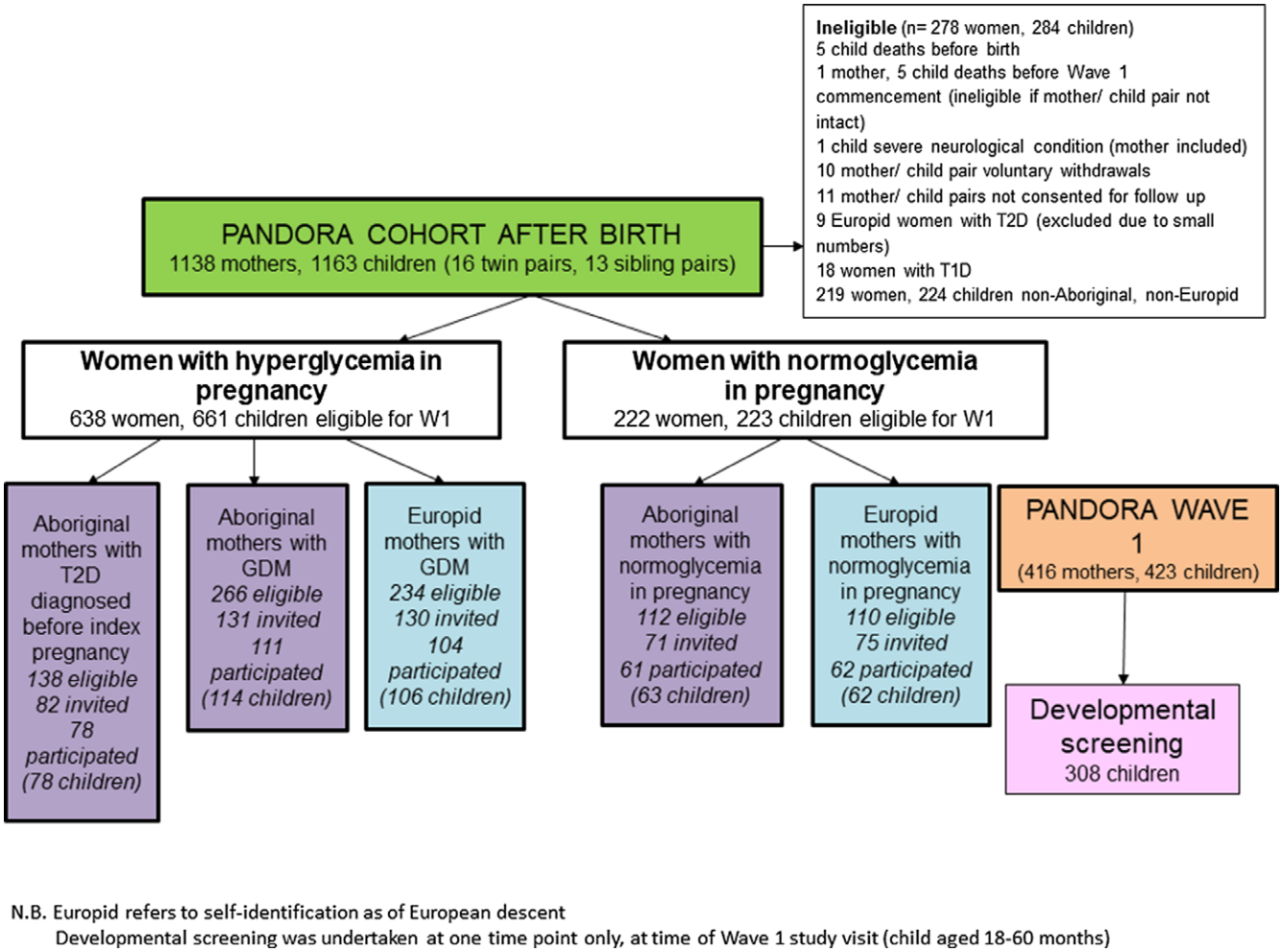

Fig. 1. PANDORA Wave 1 study participants.

Children's outcomes were categorized within each developmental domain using reference scores for age at the time of ASQ-3 completion, with "at risk" representing a score of 2 or more standard deviations (SD) below the mean achievement for age, "monitoring zone" representing a score of 1–2 SD below the mean, and "above cutoff" representing typical development.[28] For this study, scores within either the "at-risk" or "monitoring" zones were combined and defined as developmental "concern," corresponding to a score of 1 SD or more below the mean of the ASQ-3 normative data for age.

ASQ-TRAK

The ASQ-3 has been culturally adapted as the ASQ-TRAK and validated for use with Aboriginal children.[26,30,31] Within the age range of this study, it has been validated only for the following age ranges: i) 17–18 months, ii) 23–25.5 months, iii) 34.5–38 months and iv) 45–50 months, it and is adjusted for prematurity if aged less than 2 years. The tool was administered by interview, acknowledging the high prevalence of Aboriginal first languages within the NT (Table 2). As the ASQ-TRAK has only been validated at specific age ranges, developmental screening was only undertaken if a child fell within the validated four age ranges. ASQ-3 was attempted in other Aboriginal children.

Strengths and Difficulties Questionnaire (SDQ)

The **Strengths and Difficulties Questionnaire** (SDQ) is a 25 item measure of clinically significant emotional and behavioral difficulties in children across five domains, highlighting areas of difficulty in emotional regulation requiring further investigation.[32] The SDQ has been validated from 3 years of age and used in Australian Aboriginal child cohorts[33–36] to identify "at-risk" children through use of the total strengths and difficulties score,[37] derived by summing 20 of the 25 items.[32] As a subanalysis, the SDQ was completed by carers of children aged ≥3 years ($n = 101$), self-administered or by interview at participant's preference.

Statistical analysis

Statistical analyses were conducted using STATA v15 (Stata Corporation, College Station, TX, USA). Continuous and categorical child and maternal characteristics were compared by maternal glycemic status (T2D, GDM, and no hyperglycemia) using ANOVA and chi-square tests, respectively. ASQ -3/ASQ-TRAK scores were continuous variables, categorized for the purpose of description and analyses, into binary outcomes of developmental "concern" (score ≥1 SD below mean) or typical development; and "at risk" (score ≥2 SD below mean) or typical development. In the SDQ subanalysis, total score was analyzed both as a continuous

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outcome and stratified by category of risk.[37] Characteristics of those who participated in Wave 1 were also compared to those who were eligible but did not participate.

Relationships between the developmental and behavioral outcome variables and the independent variables (including maternal glycemia and ethnicity) were assessed using univariate logistic regression. Potential model variables included child factors (age, sex, prematurity (yes/no), BMI, *in utero* exposure to smoking in pregnancy (yes/no), *in utero* exposure to hyperglycemia in pregnancy (T2D/GDM/normoglycemia)); maternal factors (age, BMI, educational attainment (completion of ≤10 years vs >10 years of schooling)). Family factors included remote residence as well as self-reported maternal socioeconomic measures. These are all variables known to affect both risk of hyperglycemia in pregnancy and offspring neurodevelopment independent of hyperglycemia. As maternal educational attainment was the socioeconomic measure most consistently associated with developmental outcomes on univariable analyses, it was used in multivariable regression analyses as a marker of socioeconomic status. Interactions were explored between maternal glycemic status and each of the socioeconomic measures, by adding into the models glycemic status by socioeconomic measures as multiplicative terms. A chi-square test for the difference in deviance between the models with and without multiplicative terms was used to assess the statistical significance of the interaction.

All variables with p value ≤0.2 on univariate analysis were included in the multivariable model building process. Only variables with p value ≤0.1 on stepwise multivariable analysis were included in the final model for each outcome, with the exception of maternal hyperglycemia in pregnancy (included regardless of *p*-value, being the variable of interest), maternal ethnicity (also included regardless of *p*-value, acknowledging both that Europid women with T2D were excluded and that ethnicity likely represents unmeasured socioeconomic factors) and child age and sex. This *p* value was chosen to include variables that may have an important confounding effect on other exposures and to explore variables that, although non-significant, have a *p*-value that might indicate a significant effect with a larger sample. Therefore, the final model used differed for each developmental outcome (Fig. 2).

Ethics

The study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, and the Central Australian Human Research Ethics Committee.

Results

A total of 308 children (158 Aboriginal (44% ASQ-TRAK, 56% ASQ-3), 150 Europid), underwent developmental screening and were included in this analysis. There were no demographic differences among Aboriginal mothers who participated in Wave 1 compared to Aboriginal women who were eligible but did not participate (Supplementary Table 1). Participant Europid mothers were slightly older and had a lower BMI than non-participant Europid mothers. Of the 158 Aboriginal mothers, 48 (30%) had T2D in pregnancy, 72 (46%) had GDM, and 38 (24%) normoglycemia. Of Europid women, 90 (60%) had GDM and 60 (40%) normoglycemia.

Demographic characteristics according to maternal glycemic status and ethnicity

Aboriginal and Europid Wave 1 children (Table 1) showed similar sex distribution but Aboriginal children were older than Europid children. Europid mothers had a lower BMI, delivered later and a lower proportion of Europid children were born prematurely. Aboriginal women, regardless of maternal glycemic status, were more likely to have smoked during pregnancy and live in a remote area and less likely to have completed upper secondary schooling.

Europid women with hyperglycemia delivered earlier than Europid women without hyperglycemia. Aboriginal women with hyperglycemia delivered earlier than Aboriginal women with normoglycemia, with the highest risk among those with T2D, were older, and had lower educational attainment (schooling duration ≤10 years). Rates of inductions tended to be higher among women with T2D or GDM than normoglycemia though this did not reach significance (T2D 36%, GDM 39%, normoglycemia 28%, $p = 0.15$).

Association between maternal hyperglycemia in pregnancy and child developmental risk (Supplementary Table 2)

For both Aboriginal and Europid mothers, maternal glycemic status in pregnancy was significantly associated with developmental "concern" (i.e. score within "at-risk" or monitoring zones for age, ≥1 SD below mean for age) in the fine motor domain and probability of being "at risk" (score ≥2 SD below mean) in at least one developmental domain. A total of 71 (23%) children were categorized as "at risk" in at least one developmental domain.

Association between socioeconomic status, maternal and child risk factors and developmental risk

Univariate analysis of developmental risk with child and maternal risk factors is outlined in Table 2.

Lower maternal educational attainment was associated with increased developmental "concern" (score ≥1 SD below mean) in all domains except fine motor, as well as increased developmental "risk" (score ≥2 SD below mean) in at least one domain (59% if schooling duration ≤10 years, 18% if schooling duration >10 years, $p < 0.001$). Children whose mother's main income source was government welfare payments were at increased "concern" in all domains except gross motor, and of being "at risk" in at least one domain (40% if government welfare income source, 11% if employment, 11% if other income source, $p < 0.001$). Children whose parent/s owned their house or whose mothers were employed (in any hourly capacity) at the time of Wave 1 visit were at decreased developmental "concern" in all domains except gross motor, and less likely to be "at risk" in at least one domain (6% if owner occupier, 23% if renting, 36% if living with family, $p < 0.001$; 11% if mother in employment, 34% if mother in home duties, 41% if mother unemployed, $p < 0.001$).

There was a significant interaction between maternal education and diabetes type within the fine motor domain ($p = 0.02$), with higher maternal education reducing the risk associated with maternal diabetes. The odds ratio for offspring of women with T2D and less than 10 years of schooling having fine motor "concern" was 2.70 (95% CI 0.63–11.39), compared to 1.71 (0.12–23.94) for offspring of women with T2D and at least 10 years of schooling, however this was not significant ($p = 0.77$). There was no significant interaction between diabetes status and any other socioeconomic measure in any developmental domain.

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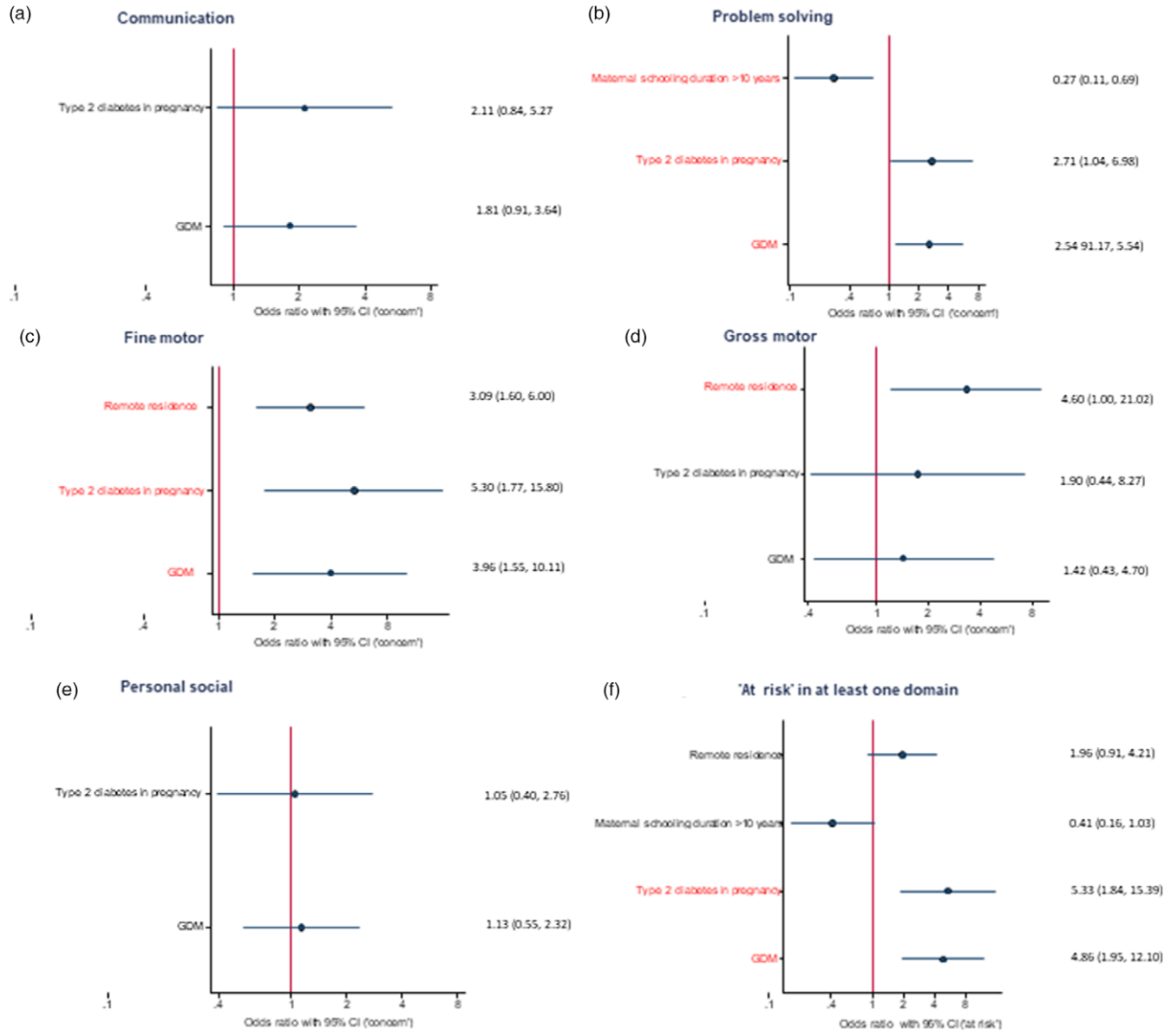

Fig. 2. Multivariable analysis of factors impacting on likelihood of "concern" result on ASQ-3/ASQ-TRAK in: (a) Communication domain. (b) Problem-solving domain. (c) Fine motor domain. (d) Gross motor domain. (e) Personal-social domain. (f) Likelihood of "at-risk" result in at least one developmental domain.

Multivariable analysis including all risk factors – association between maternal glycemic status and child developmental risk

The association between potential model variables and developmental "risk" is outlined in Supplementary Table 3. Variables included in the final models, other than maternal hyperglycemia, ethnicity and child age and sex differed for each developmental outcome and are shown in Figure 2. Covariates that remained significant in the final models, with variation noted between developmental outcomes, included child sex, remote residence, maternal education and maternal ethnicity.

In multivariable analysis (Fig. 2), after adjustment for socioeconomic measures, maternal glycemic status was associated with increased developmental "concern" (score ≥1 SD below mean) in the fine motor and problemsolving domains, as well as increased "risk" (score ≥2 SD below mean) in at least one domain. The only socioeconomic measures to remain significant in the final models were remote residence in the fine motor domain and maternal education in the problem-solving domain.

Of note, of the 72 Aboriginal women with GDM, 17 (24%) had likely T2D first diagnosed in pregnancy, using oral glucose

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Table 1. Demographic characteristics of PANDORA Wave 1 participants by study group

	Aboriginal mother					Europid mother			
	T2D ($n = 48$)	GDM ($n = 72$)	No hyperglycemia ($n = 38$)	Comparison within Aboriginal group by maternal glycemic status*	Total ($n = 158$)	GDM ($n = 90$)	No hyperglycemia ($n = 60$)	Comparison within Europid group by maternal glycemic status*	Total ($n = 150$)
Child characteristics									
Age (months)	35.4 (12.2)	34.5 (10.7)	32.0 (12.4)	0.38	34.2 (11.6)	33.4 (8.2)	27.4 (7.9)	<0.001	31.0 (8.6)
Sex (male)	19 (40)	34 (47)	23 (61)	0.15	76 (48)	46 (51)	37 (62)	0.20	83 (55)
Gestational age at birth (weeks)	36.6 (2.4)	38.0 (1.8)	39.6 (1.1)	<0.001	37.9 (2.2)	38.8 (1.4)	39.5 (1.3)	<0.01	39.1 (38.8)
Premature birth (<37 weeks)	18 (38)	12 (17)	0 (0)	<0.001	28 (18)	9 (10)	1 (2)	0.05	10 (7)
BMI Z score	0.42 (1.27)	0.24 (1.29)	0.36 (1.15)	0.72	0.32 (1.25)	0.68 (0.86)	0.98 (1.04)	0.12	0.80 (0.95)
Maternal characteristics									
Maternal age (years)	35.1 (5.4)	32.3 (6.1)	27.6 (4.7)	<0.001	32.0 (6.2)	34.6 (5.8)	34.3 (5.4)	0.72	34.5 (5.6)
BMI at first antenatal visit (kg/m2)	31.3 (5.6)	29.7 (8.3)	25.0 (6.8)	<0.001	29.0 (7.6)	28.2 (6.6)	24.6 (4.3)	0.28	28.0 (6.5)
Remote residence	31 (65)	47 (65)	24 (63)	0.98	102 (65)	3 (3)	0 (0)	0.98	3 (2)
Schooling duration ≤10 years	13 (28)	10 (14)	3 (8)	0.04	26 (17)	1 (1)	0 (0)	0.41	1 (1)
English as primary language	14 (29)	36 (50)	19 (50)	0.05	89 (56)	89 (99)	59 (98)	0.77	2 (1)
Pregnancy characteristics									
Glycated hemoglobin (HbA1c) (mmol/mol)	61 [54, 66]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Fasting glucose (mmol/l)	n/a	4.9 [4.7, 5.1]	4.3 [4.1, 4.4]	<0.001	n/a	4.7 [4.5, 4.8]	4.2 [4.2, 4.3]	<0.001	n/a
One hour glucose (mmol/mol)	n/a	9.8 [9.2, 10.3]	7.0 [6.5, 7.5]	<0.001	n/a	9.2 [8.8, 9.6]	6.8 [6.4, 7.2]	<0.001	n/a
Two hour glucose (mmol/mol)	n/a	8.3 [7.7, 8.8]	5.9 [5.6, 6.3]	<0.001	n/a	8.4 [8.1, 8.7]	5.5 [5.2, 5.8]	<0.001	n/a
Smoking in pregnancy	17 (35)	25 (36)	13 (35)	0.99	52 (68)	13 (14)	11 (18)	0.52	24 (32)

Data are mean (SD), mean [95% CI] or *n* (%).
Note: The same measures of severity are not available across categories of maternal hyperglycemia (GDM vs T2D), with oral glucose tolerance test data available for women with GDM and glycated hemoglobin data available for women with T2D in pregnancy.
Total number of women presented in this table, $n = 302$.
Total number is reduced for specific variables: HbA1c, $n = 45$ (of 48 women with T2D); oral glucose tolerance test results, $n = 155$ of 162 women with GDM, 98 of 98 women with normoglycemia; BMI at first antenatal visit, $n = 178$; gestational weight gain, $n = 131$; smoking in pregnancy, $n = 232$; maternal educational attainment, $n = 296$. Mean gestational age at time of BMI measurement 14.4 (0.4) weeks.
Women with likely T2D, first diagnosed in pregnancy, were included in the GDM group for the main analysis ($n = 17$). Sensitivity analyses were then performed as follows, i) excluding these women, ii) including these women in the T2D group. Sensitivity analyses were also performed excluding twins and siblings ($n = 6$) and recategorising children born to an Europid mother and Aboriginal father ($n = 6$).
*p value.

Table 2. Univariate analysis of associations between developmental "risk" and potential variables for inclusion in multivariable modeling

	'At risk' in any domain		Communication 'typical'		Problem solving 'typical'		Fine motor 'typical'		Gross motor 'typical'		Personal-social 'typical'	
Independent variables	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Child variables												
Premature birth <37 weeks	1.59 (0.76, 3.33)	0.22	1.10 (0.81, 0.50)	0.81	0.47 (0.24, 0.96)	0.04	0.73 (0.32, 1.71)	0.47	1.24 (0.28, 5.60)	0.78	1.40 (0.52, 3.76)	0.78
Female sex	0.56 (0.32, 0.97)	0.04	2.16 (1.25, 3.73)	0.01	1.91 (1.11, 3.27)	0.02	1.79 (0.96, 3.36)	0.07	1.48 (0.56, 3.91)	0.44	3.00 (1.52, 5.92)	<0.01
Age (months)	1.05 (1.02, 1.07)	<0.001	0.99 (0.97, 1.02)	0.55	0.95 (0.93, 0.98)	<0.001	0.96 (0.94, 0.99)	0.01	1.01 (0.97, 1.06)	0.57	1.00 (0.97, 1.03)	0.89
Maternal variables												
Age (years)	0.99 (0.94, 1.03)	0.54	1.07 (1.02, 1.12)	<0.01	1.02 (0.97, 1.06)	0.42	0.99 (0.95, 1.05)	0.84	0.99 (0.92, 1.07)	0.82	1.05 (1.00, 1.11)	0.06
BMI (kg/m^2)	1.03 (0.99, 1.07)	0.11	0.97 (0.94, 1.01)	0.11	0.97 (0.94, 1.01)	0.15	0.98 (0.94, 1.03)	0.43	1.02 (0.95, 1.10)	0.54	0.99 (0.95, 1.04)	0.75
Aboriginal ethnicity	6.79 (3.47, 13.29)	<0.001	0.20 (0.11, 0.36)	<0.001	0.13 (0.06, 0.25)	<0.001	0.34 (0.18, 0.66)	<0.01	0.47 (0.17, 1.26)	0.13	0.38 (0.20, 0.73)	<0.01
Schooling duration >10 years	0.15 (0.06, 0.34)	<0.001	3.47 (1.54, 7.80)	<0.01	8.19 (3.48, 19.25)	<0.001	2.01 (0.80, 5.07)	0.14	3.44 (1.04, 11.40)	0.04	2.57 (1.05, 6.29)	0.04
Remote residence	4.93 (2.78, 8.73)	<0.001	0.28 (0.16, 0.48)	<0.001	0.21 (0.12, 0.37)	<0.001	0.28 (0.15, 0.53)	<0.001	0.29 (0.11, 0.77)	0.01	0.54 (0.29, 1.01)	0.06
Pregnancy variables												
Hyperglycemia in pregnancy												
normoglycemia	Ref		Ref		Ref		Ref		Ref		Ref	
GDM	3.32 (1.53, 7.18)	<0.01	0.74 (0.40, 1.37)	0.34	0.50 (0.25, 0.97)	0.04	0.15 (0.05, 0.42)	0.01	0.63 (0.19, 2.08)	0.45	0.92 (0.46, 1.84)	0.82
T2D	8.90 (3.64, 21.73)	<0.001	0.38 (0.17, 0.82)	0.01	0.17 (0.08, 0.38)	<0.001	0.27 (0.11, 0.67)	<0.001	0.35 (0.09, 1.37)	0.13	0.65 (0.27, 1.59)	0.35
Smoking in pregnancy	1.42 (0.77, 2.60)	0.26	0.83 (0.45, 1.50)	0.53	0.65 (0.36, 1.16)	0.14	0.70 (0.36, 1.38)	0.31	0.46 (0.17, 1.26)	0.13	0.87 (0.43, 1.75)	0.69

N.B. Only variables with p value ≤0.2 on univariate analysis were included in multivariable modeling for each developmental outcome, with exception of maternal hyperglycemia in pregnancy and ethnicity, and child age and sex. Odds ratio for T2D and GDM use normoglycemia as the comparison group.
Risk any domain: maternal BMI, maternal educational attainment, remote residence.
Communication: maternal age, maternal BMI, remote residence, maternal educational attainment.
Problem-solving: maternal BMI, remote residence, maternal educational attainment, premature birth, maternal smoking in pregnancy.
Fine motor: remote residence, maternal educational attainment.
Gross motor: remote residence, maternal education attainment, maternal smoking in pregnancy.
Personal-social: maternal age, remote residence, maternal educational attainment.

tolerance test or HbA1c criteria.[38] Sensitivity analyses regarding i) recategorisation of women's glycemic category (for the group with likely T2D first diagnosed in pregnancy), ii) twins, and iii) children with Europid mother and Aboriginal father demonstrated no differences in outcomes, in univariate or multivariable analysis.

Association between maternal characteristics and risk of emotional and behavioral difficulties of children

Of 136 children aged 36 months or more in Wave 1, 101 carers (74% of eligible children) completed the SDQ (67 Aboriginal, 34 Europid).There were no significant differences by maternal glycemic status, in SDQ total score, or category of risk of clinically significant emotional or behavioral difficulties (Supplementary Table 3).

Discussion

We describe adverse developmental risk of 18–60 month old children living in the NT, Australia, with high rates of exposure to maternal T2D, as well as GDM, and approximately 50% of the cohort being Aboriginal. Within our cohort, 23% (71) children were categorized as "at risk" (i.e. ≥2 SD below mean for age) in at least one developmental domain. We demonstrate in the context of a multitude of other factors impacting on developmental risk, that maternal glycemic status also influences risk within this population. Firstly, after adjustment for child and maternal variables, and socioeconomic measures, maternal hyperglycemia (both T2D and GDM) was associated with increased developmental "concern" (score ≥1 SD below mean) in the fine motor and problem-solving domains. Both T2D and GDM were also associated with increased "risk" (score ≥2 SD below mean) in at least one domain. Secondly, socioeconomic factors likely also influence developmental risk.. Notably, this is the first study to use a culturally appropriate developmental screening tool validated within the Aboriginal Australian population to explore the association between exposure to hyperglycemia in pregnancy and child development.

We reported that maternal glycemic status is associated with developmental "risk," in contrast to Campribi Robles' assertion,[16] though we note the mixed evidence from previous studies.[11,13,39] Our finding that both T2D and GDM increased "concern" in the fine motor and problem-solving domains is consistent with previous data, suggesting that *in utero* exposure to hyperglycemia may particularly increase the risk of lower cognitive scores, inattention, hyperactivity and poor fine motor skills.[13] This highlights that maternal hyperglycemia is a critical target for intervention to optimize developmental trajectories.

We were unable to analyze further by degree of maternal hyperglycemia in pregnancy, and note that 19% of Aboriginal women classified with GDM likely had T2D, first diagnosed in pregnancy, although sensitivity analysis excluding these women did not alter our findings. Xiang's study[11] is one of the few with a large cohort of women with T2D, although limited by retrospective design, and suggested higher incidence of autism in offspring of women with T2D versus GDM.

In our novel study, 16% of children were born to mothers with T2D in pregnancy. This is in contrast to previous studies, the majority of which have explored the association between GDM and developmental risk.[39–41] Analysis of differences in developmental risk post exposure to *in utero* T2D or GDM is important due to the more severe metabolic changes seen in T2D in pregnancy, and hyperglycemia being present preconception and during early pregnancy. T2D in pregnancy may be associated with developmental risk in offspring through neurocognitive influences on the developing brain,[6,42] and/or through ongoing impacts on the child, reflecting underlying food insecurity or poverty. Of note, our study demonstrated maternal BMI to have no association with developmental risk in children independent of maternal hyperglycemia.

Our study highlights the likely role of socioeconomic factors on the developmental trajectories of children; higher maternal educational attainment was protective in some domains. However, in other domains, this impact was not apparent and maternal glycemic status had a strong impact. The women with T2D in our study were more likely to have lower educational attainment, have government welfare payments as their main income source, and be unemployed, than women with GDM or normoglycemia, and were less likely to own their house. This suggests that the risk of hyperglycemia in pregnancy is itself related to the cumulative impact of socioeconomic factors and builds on reports of developmental disparity in the context of socioeconomic vulnerability.[3,10] This is consistent with the previously reported association between diabetes and low SES internationally and in our context.[19,43,44] We demonstrated that multiple measures of low SES (such as lower maternal educational attainment and receiving government welfare payments) were associated with developmental "concern" and "risk," and remote residence and maternal education remained significant in multivariable analysis. However, no significant interaction was demonstrated between maternal educational attainment and diabetes type with respect to developmental outcomes, with the exception of fine motor skills. This points to possible interventions to improve developmental trajectories, focusing on structural inequities, maternal education and employment.

Higher maternal education has been shown to be protective within multiple developmental domains for Aboriginal children, likely serving as a proxy for structural determinants of health inequality.[38,39] Our study indicates that maternal glycemic status is an important marker of risk for women with low educational attainment, suggesting a possible target for intervention. Women with chronic conditions such as diabetes are likely to benefit from strategies that address systemic inequities, increase their health literacy, and improve support, particularly at key time points such as preconception, during pregnancy, and in the early childhood of their offspring. Other factors that may be protective against the impact of *in utero* hyperglycemia include breastfeeding, strong attachment to carers, positive family engagement and support, and exposure to structured learning environments in early childhood.[45]

The relationship between developmental "risk" and low SES makes it difficult to isolate any direct causal effect of *in utero* exposure to hyperglycemia in this study.[16,40,46] US data demonstrate a 14-fold additive risk of GDM in combination with low SES for attention deficit hyperactivity disorder diagnosis at 6 years of age,[17] although only small numbers were involved. The US setting is also very different to the remote Australian context, where there are stark socioeconomic and cultural differences, particularly among urban and remote, and Aboriginal and non-Indigenous families.[47] This may mask the developmental impact of maternal hyperglycemia in the context of key basic health and developmental needs not being met. Remote residence may serve as a proxy indicator of a range of markers of socioeconomic deprivation including (but not limited to): housing adequacy, food security, health literacy, multiple measures of socioeconomic status, such

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as employment, and access to health services. Policies and programs that support and empower women in remote communities, improve infrastructure and service delivery, and enable healthy lifestyles for both themselves and their children, are critical to improving health and preventing intergenerational transmission of chronic conditions.

Our finding of an independent association between maternal glycemia in pregnancy (both T2D and GDM) and concern (score ≥1 SD below mean for age) in the fine motor and problem-solving domains, as well as an "at-risk" (score ≥2 SD below mean for age) result in any domain, is important in the context of these substantial socioeconomic inequities. It indicates the need for effective interventions to both improve maternal glycemic profile in women diagnosed with T2D in pregnancy or GDM and prevent the development of T2D or GDM among women. These interventions will potentially not only improve maternal health but may also optimize the developmental trajectories of their offspring. Potential interventions to prevent the development of T2D or GDM at a young age, as well as prevent intergenerational transmission of risk, include the promotion of breastfeeding,[48,49] improvements in food security, early detection of hyperglycemia in pregnancy through improved antenatal and primary health care services, investment in adolescent and preconception health, and strategies targeting childhood obesity. It is also critical to address underlying socioeconomic inequities, educational disadvantage and the ongoing effects of intergenerational trauma, grief, and loss.

These findings of maternal hyperglycemia being an important risk factor in the developmental trajectories of children are in contrast to a previous meta-analysis[16] suggesting inconclusive evidence of any effect if women with and without diabetes in pregnancy come from similar cohorts. That analysis was limited by the small number of studies adjusting for parental socioeconomic status or educational attainment, and the grouping of all types of diabetes together in the analysis.[16] Swedish data demonstrate differential effect on educational achievement by maternal diabetes status only between non-siblings, suggesting that the association between maternal diabetes in pregnancy and offspring cognition may be more driven by shared genetic and environmental characteristics,[46] in contrast to our findings.

We reported no difference in the risk of clinically significant emotional or behavioral difficulties by maternal glycemic status. This is in contrast to other Australian studies,[50,51] and may relate to the lower age of children in our study (preschool age), with SDQ completed by mothers. There may also be inherent bias from some women completing SDQ by interview rather than self-completion. Emotional and behavioral difficulties may also become more apparent over time, with some behavioral diagnoses recommended to only be diagnosed after school commencement age.

A strength of our study is the birth cohort context, allowing prospective detailed information regarding maternal diabetes status, maternal adiposity, and multiple measures of SES to be elicited, overcoming some of the inconsistencies in the literature regarding glycemia in pregnancy and developmental risk.[16] A second strength is the high proportion of women with T2D, in contrast to previous studies which have been restricted to comparison of women with GDM, type 1 diabetes or normoglycemia.[16] Most previous studies have also not differentiated by type of maternal diabetes in terms of offspring developmental or neurocognitive outcomes, making it difficult to assess the differential impact of different time points of *in utero* exposure to hyperglycemia. In contrast to another Australian study[52] and in response to criticisms of previous studies that have not explored the effect of maternal adiposity,[53] we have reported that maternal BMI had no association with developmental "risk." By identifying child developmental issues early through screening, the study has also helped facilitate earlier treatment, with referrals to primary and specialist health care teams, and additional developmental delays or deficits may be prevented.

A limitation of the study is the reliance on developmental screening, as opposed to developmental assessment, meaning that only risk of potential developmental issues can be identified, rather than their extent. Attempting developmental screening is difficult because of its dynamic nature, and the interrelation between developmental domains.[54] Screening at a single time point may also not capture skills and abilities in the higher range of performance or over time.[55,56] However, while the ASQ-3 was designed and validated for use as a developmental screening tool,[28] it has been used in various studies for different purposes, including as a developmental outcome measure in five developmental domains.[57,58]

The ASQ-TRAK is the first developmental screening tool adapted for use in the Australian Aboriginal remote population,[30] acknowledging that, historically, very few developmental screening tools have been developed or tested with linguistically or culturally diverse samples of children.[56,59] A recent validation study comparing results of ASQ-TRAK to full developmental assessment, using the Bayley-III, demonstrated moderate correlation in communication, gross motor, fine motor, and problem-solving domains, with 90% agreement.[30] The negative predictive value of 96% suggests that an "above cutoff" result in ASQ-TRAK likely represents a typically developing child. However, the lower positive predictive value of 50% suggests that some children will be falsely identified in the "at-risk" zone on ASQ-TRAK who will be typical on full developmental assessment.

Another limitation is the possibility that participants, including women without hyperglycemia in pregnancy, are not representative of the wider NT population due to the cohort nature of our study. However, of those on the NT Diabetes in Pregnancy Register, 54% participated in PANDORA, and there were no significant differences in maternal age, ethnicity, or remote locality when compared to the cohort group.[25] Additionally, as the study sample size was not calculated for the purpose of addressing differences in developmental outcomes, it may have been underpowered for some of the comparisons presented. This also limited further exploration of the association between developmental risk, maternal glycemic status, and maternal educational attainment. Further work is required to explore differential risk for offspring exposed to T2D in pregnancy compared to GDM. Following our cohort into later childhood will allow assessment of more subtle neurocognitive and behavioral differences, in the context of more complex neurodevelopmental requirements with increasing age. Assessment of outcomes using psychometric measures, rather than screening of developmental status, will also support more precise and differentiated evaluation.

Conclusion

In conclusion, maternal hyperglycemia was associated with increased developmental concern, though whether the timing of *in utero* exposure is additive to underlying socioeconomic vulnerability remains unclear. While children may improve in these skills over time, prevention of maternal hyperglycemia in pregnancy is a potential point of intervention to improve developmental trajectories of children, particularly in the context of such high rates of maternal hyperglycemia among Aboriginal women.

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Addressing wider social determinants and inequities, and building on the strengths of Aboriginal culture and families, is likely to significantly improve developmental outcomes, including in children born to mothers with hyperglycemia in pregnancy. Policies and programs that support and empower women and improve access to education, food security, housing and services are likely to have beneficial impacts on offspring and improve intergenerational outcomes. Further work is required to establish whether developmental and behavioral risk changes over time, to understand the ongoing impact of food security and nutrition on child development after a pregnancy complicated by hyperglycemia, and to establish effective interventions to reduce risk of maternal hyperglycemia in pregnancy.

Supplementary materials. For supplementary material for this article, please visit https://doi.org/10.1017/S2040174422000101

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