Anaemia among Aboriginal and Torres Strait Islander children and their mothers in Far North Queensland

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'The first thousand days between a woman's pregnancy and her child's second birthday offers a unique window of opportunity to shape healthier and more prosperous futures.'

Professor Kerry Arabena

(quoted in the Closing the Gap Report 2019, p 29)

https://ctgreport.niaa.gov.au/sites/default/files/ctg-report-20193872.pdf?a=1

Anaemia definition, main causes and outcomes

Anaemia is diagnosed when the concentration of haemoglobin falls below established cut-off values. When the haemoglobin concentration decreases, the capacity of the blood to carry oxygen to tissues is compromised, resulting in symptoms such as fatigue, reduced physical work capacity, and shortness of breath, among others. p2

…. Nutritional deficiencies, diseases and genetic haemoglobin disorders are the most common contributors to anaemia. p2

….Anaemia has been associated with negative outcomes in several population groups – including maternal mortality, low birth weight and premature birth, as well as delayed child development; as yet, a causal link has not been established for all outcomes, despite strong biological plausibility. p5

World Health Organization. Nutritional Anaemias: Tools for Effective Prevention and Control Geneva: 2017 (Chapter 1, reference 11)

Abstract

Introduction: Anaemia in early life – defined as low levels of haemoglobin - is associated with persistent deficits in early childhood development. Effective interventions to prevent and/or treat early childhood anaemia are available that have been shown to attenuate this developmental deficit. This research was undertaken to provide information about anaemia among Aboriginal and Torres Strait Islander children and their mothers in Far North Queensland, to clarify if such interventions are required in this setting. High rates of anaemia among Aboriginal and Torres Strait Islander mothers and children has been reported from elsewhere in northern Australia but information was lacking for Far North Queensland.

Methods: Linked de-identified information was secured from four Queensland Health data collections for children born between 2006 and 2010, and their mothers (n = 2,195 mother and child pairs). Where available, health information was linked to information on indicators of early childhood development from the triennial Australian Department of Education Australian Early Development Census (AEDC).

Key results: Just over half the mothers with measurements of haemoglobin (n = 2,076) had anaemia in pregnancy (54.5% anaemic; 95%CI 49.9%, 56.7%). Longitudinal information on child haemoglobin levels was available for children usually resident in remote communities only (n = 708). More than half of these children were anaemic at age 6-23 months (61.3%; 95% CI 57.7%, 64.9%). Of these 708 children, 250 were assessed during the triennial Australian Early Development Census (AEDC) on five domains of early childhood development at around age five years. Compared to children who had not been anaemic (n = 107) at age 6-23 months, children who had been anaemic (n = 143) were at increased risk of developmental vulnerability on two or more AEDC domains (OR 2.2; 95% CI 1.2, 4.1 p = 0.016) at around age five years.

Conclusion: Anaemia in pregnancy and early life is prevalent among Aboriginal and Torres Strait Islander mothers and children in Far North Queensland. This early childhood anaemia is associated with persistent developmental deficits. Effective interventions that prevent early childhood anaemia are available and may improve early childhood development and subsequent educational attainment in this setting.

List of Publications Included in This Thesis

Chapter #, Paper #	Publication, nature and extent of intellectual input from each author including the candidate
Chapter 2, Paper 1	Leonard D, Buettner P, Thompson F, Makrides M, McDermott R. Linking 'data silos' to investiate anaemia among Aboriginal and Torres Strait Islander mothers and children in Far North Queenland. ANZJPH. 2018;42(5):256-62. *DL conceived the study methodology, secured the necessary approvals and the linked de-identified data file. FT guided the merging of the linked data and data cleaning and variables definitions processes, checking all results. DL wrote the paper; all authors contributed to the further development of the manuscript and responses to reviewers.*
Chapter 3, Paper 2	Leonard D, Buettner P, Thompson F, Makrides M, McDermott R. Anaemia in pregnancy among Aboriginal and Torres Strait Islander women of Far North Queensland: a retrospective cohort study. Nutrition and Dietetics. 2018. *DL undertook descriptive and bivariate statistical analysis; PB and DL undertook multi-variable analysis, processes and findings were checked by FT. DL wrote the paper; all authors contributed to the further development of the manuscript and responses to reviewers.*
Chapter 4, Paper 3	Leonard D, Buttner P, Thompson F, Makrides M, McDermott R. Anaemia in early childhood among Aboriginal and Torres Strait Islander children of Far North Queensland: a retrospective cohort study. Aust N Z J Public Health. 2019. *DL undertook descriptive and bivariate statistical analysis; PB and DL undertook multi-variable analysis, processes and findings were checked by FT. DL wrote the paper; all authors contributed to the further development of the manuscript and responses to reviewers.*
Chapter 5, Paper 4	Leonard D, Buttner, P., Thompson, F., Makrides, M., McDermott, R. Early childhood anaemia more than doubles the risk of developmental vulnerability at school-age among Aboriginal and Torres Strait Islander children of remote Far North Queensland; findings of a retrospective cohort study. Submitted to Nutrition and Dietetics (July 2019)

Chapter #, Paper #	Publication, nature and extent of intellectual input from each author including the candidate
	DL undertook descriptive and bivariate statistical analysis; PB and DL undertook multi-variable analysis, processes and findings were checked by FT. DL wrote the paper; all authors contributed to the further development of the manuscript to submission stage.
Appendix 1	Aquino D, Leonard D, Hadgraft N, Marley J. High prevalence of early onset anaemia amongst Aboriginal and Torres Strait Islander infants in remote northern Australia. Australian Journal of Rural Health. 2018. *DA led the statiscal analysis and the manuscript development. JM checked analysis and findings. All authors contributed to manuscript development and revision.*
Appendix 2	Leonard D, Aquino D, Hadgraft N, Thompson F, Marley J. Poor nutrition from first foods: a cross sectional study of complementary feeding of infants and young children in six remote Aboriginal communities across northern Australia Nutrition & Dietetics. 2017;74(5):436-45. *DL led the statiscal analysis and led the manuscript development. FT checked analysis processes and findings. All authors contributed to manuscript development and revision.*

Formatting notes: three chapters in this PhD thesis are published reports complete with references. Consistent with this, the references throughout the thesis are included at the end of each chapter.

Each of these three publications includes figures, tables and supplementary tables. In the processes of formatting this thesis, lists of tables etc. have been generated but these lists do not include those elements included in the three publications as these publications were in pdf format. Instead these have been included in the list of tables etc. as 'List of Tables in article….., List of Figures in article…..' etc.

This inclusion of these publications means there is some duplication in the supplementary tables for three chapters. Unfortunately, this is necessary to maintain consistency of cross-referencing within each chapter.

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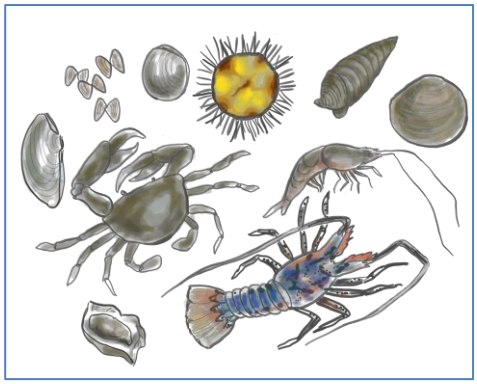
Foreword Chapter 1

This thesis describes research into anaemia among Aboriginal and Torres Strait Islander children and their mothers of Far North Queensland. In Chapter 1, I outline the rationale for this research, describing the questions raised by prior work that led to this research. That prior work highlighted the lack of information about anaemia in Far North Queensland and also raised questions about the aetiology of anaemia in the first thousand days of life – through pregnancy up to around age two years – when anaemia is usually attributed to iron deficiency.[4]

In Chapter 1 therefore, I describe the findings of that prior work and summarise current understanding of iron metabolism and nutritional requirements for iron to illustrate why iron deficiency is the 'usual suspect' as the cause of anaemia in pregnancy and the first years of life. This description of iron metabolism includes current understanding of the role of iron in neurodevelopment in the first thousand days of life and the possible detrimental effects of iron deficiency on neurodevelopment. The interrelationship of iron status, anaemia and early neurodevelopment is a key reason why anaemia in the first thousand days of life is important – and why prevention of anaemia provides an opportunity to support neurodevelopment in early life.

In subsequent chapters, I describe the methods used for this research (Chapter 2) and key findings (Chapters 3 to 5). In Chapter 6, I present a literature review undertaken to identify options for interventions to effectively reduce early childhood anaemia. The thesis concludes with a discussion (Chapter 7) of the research findings, and recommendations for future initiatives to address early childhood anaemia and by doing so, potentially enhance early childhood development.



Julie Haysom http://www.juliehaysom.com

'Good nutrition allows children to survive, grow, develop, learn, play, participate and contribute '

UNICEF, WHO/ World Bank

Joint Child Malnutrition Estimates; key findings of the 2019 edition

https://www.who.int/nutgrowthdb/jme-2019-key-findings.pdf?ua=1

Chapter 1 Introduction and Background

1.1 Introduction

Anaemia among young children of the Aboriginal and Torres Strait Islander communities of Australia has been a long-standing concern.[6, 7,8] This research rose out of previous work to assess the feasibility and acceptability of an intervention to prevent early childhood anaemia in six remote Aboriginal and Torres Strait Islander communities across northern Australia from 2010 to 2012 - the Early Childhood Nutrition and Anaemia Prevention Pilot (ECNAPP).[9] ECNAPP was undertaken in response to community and health service concerns about early childhood anaemia and interest in prevention of anaemia. [9]

Anaemia is a condition where haemoglobin levels in the blood are lower than expected for age and sex, with adjustment for factors that also influence haemoglobin levels such as altitude and smoking.[10, 11] Across northern Australia, the same criteria are used to diagnosis anaemia in pregnancy and early life.[12,13,14] Anaemia is diagnosed in pregnancy when haemoglobin level is less than 110g/L, in babies age 6-11 months when haemoglobin level is less than 105g/L, and in young children aged 12-23 months, when haemoglobin level is less than 110g/L.[12,13,14] The consequences of anaemia include reduced physical work capacity, poor pregnancy outcomes, and compromised neurodevelopment in early life.[11,]

The diagnosis of anaemia based on level of haemoglobin does not identify the cause of anaemia. Many causes of anaemia are nutrition-related (deficiencies of iron, folate and/or vitamin B12); other causes include infections, inflammation and genetic conditions.[4] Among women and children, iron deficiency is a 'common and consistent' cause of anaemia.[11, 15]

Iron is a key nutrient in various metabolic processes but most body iron is in haemoglobin in the red blood cells. [16,] Haemoglobin plays a central role in respiration that is central to all metabolic functions.[17] Healthy adults use approximately 75-80% of their body iron in haemoglobin while infants and young children use about 90% of body iron for haemoglobin.[16, 18] Available iron is prioritised for synthesis of haemoglobin over other metabolic requirements .[16, 17]

The first thousand days of life, through pregnancy to around age two years are a period of rapid growth with concurrent rapid increases in blood volume.[19,20] Consequently

requirements for iron are particularly high during the first one thousand days of life.[19, 20] This rapid early growth includes rapid neurodevelopment.[21] Iron is a key nutrient for critical phases of neurodevelopment as well as a key component of haemoglobin.[20, 21] If iron is scarce, iron is prioritised for erythropoiesis over requirements for neurodevelopment. Insufficient iron for early neurodevelopment may have persistent detrimental consequences, reflected in outcomes such as lower educational attainment at school age.[21, 22] Iron deficiency anaemia was estimated to be the leading global cause of years lived with disability for children and adolescents in 2013.[11, 23]

The prevalence of anaemia is higher in low and middle income countries compared to more affluent countries.[24] The World Health Organization (WHO) information on global prevalence of anaemia in 2011 shows that 42.6% of children aged 6-59 months were anaemic as were 38.2% of pregnant women.[24] WHO global nutrition targets include reduction of anaemia among women of reproductive age by 50%.[25] Information from the 2011-12 Australian Health Survey shows considerably lower prevalence of anaemia in Australia; 4.5% of Australian adults were 'at risk of anaemia' with higher rates among women (6.4%) compared to men (2.5%).[26] The criteria used in this national Australian survey to define 'at risk of anaemia' based on low haemoglobin levels are the same criteria that WHO uses to define anaemia.[26]

In many countries, including affluent countries such as Canada, the United States and Australia, anaemia is higher among the Indigenous populations compared with the general population.[27] This pattern was also seen in Australia. Among Australian Aboriginal and Torres Strait Islander adults, 7.6% were at risk of anaemia, close to twice the prevalence (4.5%) among non-Indigenous Australians (age adjusted rate ratio 1.9).[28] More Australian Aboriginal and Torres Strait Islander women compared to men (10.3% v 4.8%) were at risk of anaemia and more Aboriginal and Torres Strait Islander people in remote compared to non-remote locations (10.1% v. 6.9%).[28]

Baseline information collected for evaluation of ECNAPP revealed some findings that were unanticipated at that time, including a high prevalence of early childhood anaemia (n = 189, 41.7% at age 6-23 months) and early onset of anaemia.[29] Among the 163 babies with a haemoglobin measurement at 6-8 months, 91 (56%) were anaemic.[9] Among those babies (n

= 84) with haemoglobin measurements recorded before age 6 months, 25% were already anaemic.[29] Research conducted in two remote communities elsewhere in the Northern Territory at around the same time, reported that among babies (n = 398) born between 2004 and 2006, 68% were anaemic at age 6-12 months.[30] In those two communities, half (50%) of the mothers (n = 384) who gave birth between 2004 and 2006, had anaemia in pregnancy.[31]

These reports indicated that Aboriginal and Torres Strait Islander pregnant mothers, infants and young children were iron deficient during the rapid neurodevelopment of the first thousand days of life. Table 1.1 summarises information available prior to this research and shows that rates of anaemia among Aboriginal and Torres Strait Islander people, pregnant mothers and young children were higher than those experienced by the general Australian population. These figures for children are not directly comparable due to technical differences in assessment of anaemia, but do indicate a disparity in rates of anaemia experienced by Aboriginal and Torres Strait Islander people compared to other Australians.

Table 1.1

Anaemia among Aboriginal and Torres Strait Islander populations and other Australian populations (available prior to this research)

	[28]Aboriginal and Torres Strait Islander Australians >= 18 years 2012-13: % 'at risk of anaemia'	[26]All Australians 2011-12 % 'at risk of anaemia'	Aboriginal and Torres Strait Islander mothers % anaemic in pregnancy	Australian mothers % anaemic in pregnancy	Aboriginal and Torres Strait Islander infants 6-11 months / 6-12 months % anaemic	Aboriginal and Torres Strait Islander infants 6-23 months % anaemic	Aboriginal and Torres Strait Islander infants <5 years % anaemic	Australian children % anaemic
Adults	7.6%	4.5%						
Women	10.3%	6.4%						
Men	4.8%	2.5%						
Non-remote	6.9%							
Remote	10.1%							
[115] Townsville 2001-03			34.2%					
[31] NT - 2 remote communities 2004-06			50.0%					
[116] South Australia 99-2005				7.1%				
[117]Western Australia >= 18 years 2005-07				6.2%				
[118]South Australia - not supplemented 97-99				11.0%				

	[28]Aboriginal and Torres Strait Islander Australians >= 18 years 2012-13: % 'at risk of anaemia'	[26]All Australians 2011-12 % 'at risk of anaemia'	Aboriginal and Torres Strait Islander mothers % anaemic in pregnancy	Australian mothers % anaemic in pregnancy	Aboriginal and Torres Strait Islander infants 6-11 months / 6-12 months % anaemic	Aboriginal and Torres Strait Islander infants 6-23 months % anaemic	Aboriginal and Torres Strait Islander infants <5 years % anaemic	Australian children % anaemic
[9] northern Australia – 6 communities						41.7%		
[30]NT - 2 remote communities 2004-06					68.0%			
[119] Northern Territory Healthy Under Five 2014					32%%		21.0%	
[120]Adelaide age 1-2 years, 2005-07								3%
[121] various 1998 -2001								1-6%
[121]Australian children - Asian descent 1998-99								14%
[122]Australian children 1-4 years age, 1995								2%

In Australia as elsewhere, anaemia among women and young children is associated with food insecurity and poverty.[32, 33] Food costs are particularly high in remote settings, with commonly purchased items costing 50-60% more in remote stores than in city supermarkets.[34] Remote store policies may mean that this cost differential is less for some products such as fresh fruit and vegetables but the cost of these healthy foods remains higher than in city supermarkets.[34] For low income households in remote central Australia, current food costs require close to 50% of household income, compared to 31% of income for an equivalent low income household in an urban settings.[35, 36] More Aboriginal and Torres Strait Islander people (22%) especially those living in remote settings (31%) report food security issues, compared to other Australians (3.7%).[37]

The ECNAPP findings and concurrent findings from the Northern Territory (Bar-Zeev et al[30, 31]) highlighted the lack of information about anaemia among Aboriginal and Torres Strait Islander mothers and children across Far North Queensland. Information from the paediatric outreach service for Far North Queensland, collected between 2001 and 2006, showed that among children referred to that service (n = 3,562, aged birth to 18 years); 8.2% of Aboriginal children and 1.1% of Torres Strait Islander children were anaemic.[38] This information was limited to children referred to the service; information was not available for other children.[38] Similarly one Far North Queensland community participated in ECNAPP but information was not available for other Far North Queensland communities.[9] In addition, there was no information available in respect of anaemia of mothers during pregnancy. Anaemia of mothers in pregnancy is strongly associated with subsequent anaemia in their children.[39,40] Consequently information about anaemia in pregnancy is needed as well as information about anaemia among infants and young children, to cover the period of the first one thousand days of life.

In addition to the lack of information in respect of anaemia in Far North Queensland, the ECNAPP findings and the findings reported by Bar-Zeev et al [30, 31] raised further questions about the early onset of anaemia among the Aboriginal and Torres Strait Islander infants. In these remote communities, exclusive breastfeeding in the first months of life is the usual practice. [8,41] Breastfeeding has many well documented health benefits for babies and their mothers, and is recommended for optimal infant and young child nutrition.[42, 43] Most nutrition issues in early life become manifest after the period of exclusive breastfeeding,

when meeting high nutritional requirements from solid food given to complement breastmilk is more challenging. [44] It was a puzzle therefore why these (mostly) exclusively breastfed babies, were already anaemic at age 6 months presumably as a result of iron deficiency.

This thesis begins with background on iron metabolism, iron requirements and the reasons why iron is the 'usual suspect' as the cause of anaemia in pregnancy and early life. This information highlights the interrelationship of the iron status of a mother and the iron status of her baby and clarifies the many issues that underlie iron deficiency and anaemia of mothers and the early onset of anaemia in their babies and young children.

1.2 Background: Why Iron Deficiency is the 'Usual Suspect' as the Cause of Anaemia in Early Childhood

In this section, information is presented on iron metabolism, dietary iron requirements and the challenges of meeting the high iron requirements in pregnancy and the first years of life.

In affluent countries such as Australia, the major focus of current public health nutrition practice is on the association of poor dietary patterns with overweight, obesity and associated chronic disease.[45] In that context, a focus on any single nutrient such as iron is an anomaly; a throw-back to an earlier era of nutrition science when specific vitamins and minerals were found to resolve conditions such as goitre, scurvy and rickets.[45] But like rheumatic heart disease and trachoma, anaemia remains more prevalent among Australian Aboriginal and Torres Strait Islander people compared to other Australians (age adjusted Rate Ratio 1.9).[46, 28]

Iron has been described as a paradoxical nutrient.[47] One paradox is that iron is one of the most common elements on earth but iron deficiency is a common nutrient deficiency globally, particularly impacting on women and young children.[48,16] Another paradox is that the same characteristics that make iron an essential nutrient, mean that iron has the potential to cause metabolic damage; tightly regulated homeostatic systems help prevent this damage.[47] This section explores these paradoxes by describing normal iron metabolism at different life stages, dietary sources of iron and the challenges in achieving adequate dietary intakes of iron when requirements are high; the role of iron in neurodevelopment;

the role of iron in immunity, the challenges in assessing iron status and the current anaemia treatment protocols used in northern Australia.

Iron homeostasis; Iron is essential for life, playing a key role in oxygen transport and storage and in other metabolic functions including immunity, muscular activity and neurodevelopment.[18, 49] Most body iron is in haemoglobin, the oxygen transporter in the red blood cells and in myoglobin which holds oxygen in muscle cells until required for cellular processes.[18] In addition to cellular respiration, iron has other metabolic functions; for example iron-containing enzymes are involved in neurodevelopment in early life.[1, 21, 50]

Once absorbed, iron cannot be excreted.[47, 51] Iron homeostasis is maintained through tight regulation of iron absorption that ensure that iron requirements are met but not exceeded.[47] The same chemical characteristics of iron that are essential for respiration - switching between the ferrous (Fe++) and the ferric states (Fe+++) - also mean that iron has the potential to cause oxidant damage. [47] In normal metabolism, iron is bound to chaperone proteins in forms that will not cause damage - examples include transferrin for transport and ferritin for storage.[47]

Iron is present in food in two forms; haem iron and non-haem iron. Haem iron occurs only in foods of animal origin while non-haem iron occurs in both animal and plant foods; about 40% of the iron content of animal foods is in the form of haem iron which is more bio-available than non-haem iron.[49] Overall most (85-90%) dietary iron is in the non-haem form.[49] Bio-availability of non-haem iron is enhanced by ascorbic acid (vitamin C) and animal tissue but reduced by phytates from wholegrain cereals and legumes and by polyphenols in tea and coffee.[49]

However, a key factor determining the proportion of dietary iron that is absorbed is the iron status of the individual. A person who is iron replete will absorb relatively little; a person who is iron deficient will absorb more.[47, 16] The role of the hepcidin, a peptide produced in the liver, is central to maintaining iron homeostasis.[47] When an individual has sufficient body iron, hepcidin levels are higher and iron absorption is lower. Conversely when an individual has insufficient body iron, hepcidin levels are lower and iron absorption higher.[47] The effect of hepcidin is to provide a metabolic safety net against the detrimental effects of iron overload. This interaction between iron status and iron absorption means that

population-wide estimates of iron requirements (nutrient recommended values; EAR and RDIs) have added uncertainty. These estimates are based on generalised assumptions about iron absorption, whereas the proportion of dietary iron absorbed may vary with individual iron status (Box 1.1).[3, 47]

Box 1.1

Estimated requirements for specific nutrients are based on information from the National Health and Medical Research Council publication *'Nutrient Reference Values for Australia and New Zealand'* (published 2006, updated 2017)[3] that uses the terms EAR and RDI;

Estimated Average Requirements (EAR); a nutrient level estimated to meet the requirements of half the healthy individuals in a particular life-stage and gender group

Recommended Dietary Intake (RDI); the average dietary intake level that is sufficient to meet the requirements of nearly all (97-98%) healthy individuals in a particular life-stage and gender group

Adequate Intakes: (used when an RDI cannot be determined); the average daily nutrient intake based on observed or experimentally-determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate

These estimates are for healthy individuals; individuals with existing nutritional deficiency conditions may have higher requirements.

Box 1.1 Definitions - Estimated Average Requirements (EAR); Recommended Dietary Intake (RDI); Adequate Intakes (AI).

Iron requirements of men; The total body iron content of a healthy adult man is estimated to be about 4g.[16] This iron is accumulated from before birth through childhood and adolescence; once growth has ceased, the usual iron requirements of an adult man are low. About 75-80% of his body iron is in haemoglobin in the red blood cells, with the remainder in other body cells as myoglobin, as iron-containing enzymes and/or bound to proteins for transit (transferrin) or storage (ferritin).[16, 18] Iron metabolism is very efficient. Each day about 25-30mg of iron from senescent red blood cells and other cells is recycled.[47, 16] Daily losses of an adult man are small; about 1.0 mg of iron is lost each day, as skin and gut cells are shed.[47, 52] The amount of iron that needs to be absorbed is the amount needed to

replace these small losses.[52] Dietary requirements are higher however, as only 10-18% of dietary iron intake is absorbed; male 19 years or older Estimated Average Requirement (EAR) - 6 mg; Recommended Dietary Intake (RDI) 8 mg)[3] (Box 1.1, Figure 1.1).

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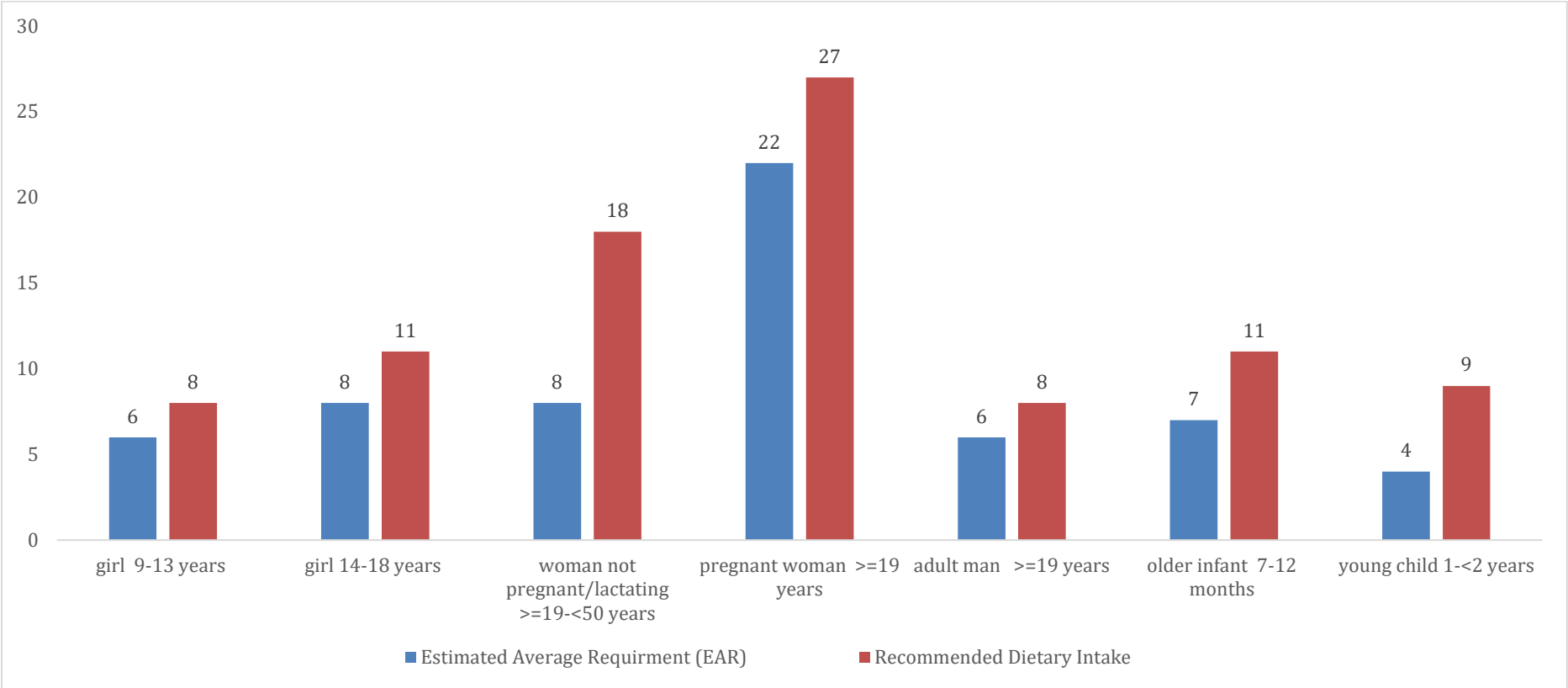

Figure 1.1 Quantity of some traditional and introduced foods (g) required to meet estimated iron requirements at age 7-12 months (sources: Estimated quantities solid food intake age 6-11 months[58]

Food composition Food Standards Australian New Zealand Nuttab 2010 Indigenous Foods ◇ Ausnut 2011-13 ; http://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/pages/default.aspx

[1] Source: NH&MRC. Nutrient Reference Values for Australia and New Zealand. Camberra: National Health and Medical Research Council, 2017.

Iron requirements of girls and women of reproductive age; As for men, iron homeostasis is tightly regulated but requirements of women of reproductive age are higher than those of men, because of the iron demands of menstruation, pregnancy and childbirth. [3 16] Iron requirements of girls increase at menarche; age 9-13 years EAR 6mg, RDI 8mg - age 14-18 years EAR 8mg, RDI 11mg (Figure 1.1).[3] On average, menstruation requires about 1.4 mg of absorbed iron per day to replace losses, in addition to losses from the skin and gut.[16] For each ml of blood lost, 0.5mg of iron is lost.[16] Those women (~10%) with heavy menstrual losses (>80 mls) are particularly at risk of iron deficiency.[16] Estimates of average dietary iron requirements for women aged 19-50 years (EAR 8 mg) are higher than those of men, while the recommended dietary intake (RDI 18mg) sufficient to meet requirements of 97-98% of healthy individuals, reflects the high requirements of the subset of women with heavy menstrual losses (Figure 1.1).[3, 16]

While menstruation ceases during pregnancy, additional iron is required for the expanding blood volume and for the growth of the placenta and the baby.[16, 40] The total iron cost of pregnancy is about 1g; for expanding blood volume ~500 mg, the foetus and placenta ~350 mg, blood loss at delivery ~250mg.[19] The net iron cost of each pregnancy has been estimated as 580 to 680 mg iron.[53] Good iron stores (~500 mg) protect women from iron deficiency in pregnancy.[51] During pregnancy, iron requirements of the foetus take precedence over the requirements of the mother but foetal iron status is compromised when the mother is iron deficient.[17] Most (~66%) transfer of iron from mother to her unborn baby occurs during the last ten weeks of pregnancy.[19] Estimated daily iron requirements in pregnancy for women over 19 years are; EAR 22 mg, RDI 27 mg (Figure 1.1).[3]

The traditional food systems of Aboriginal and Torres Strait Islander people provided many foods rich in iron - and other nutrients – such as insects, shellfish, blood, offal and lean red meat.[54, 55] Consequently, it is probable that Aboriginal and Torres Strait Islander women in traditional times, commenced pregnancy with good iron stores and ate iron-rich foods through pregnancy. These pre-agricultural diets are more nutrient dense than current diets, even those considered healthy.[44] Australian food modelling studies have shown that a healthy diet, consistent with current recommendations, will not meet requirements for iron in pregnancy, providing less than the EAR for iron in pregnancy.[5] Again, iron is a paradox in

this respect, as a healthy diet meets all other known nutritional requirements of pregnancy.[5] Iron supplements may be needed in pregnancy in addition to a healthy diet.[5]

Iron requirements of breast-fed infants to around age six months; A healthy birth weight baby born at full term to a well-nourished mother has a total body iron content of about 230-330 mg (~75mg/kg birth weight), acquired from his/her mother, mostly in the last trimester of pregnancy.[19, 20, 40] Various factors are important in determining iron status of a baby at birth; his/her mother's iron status, baby's gestational age at birth, baby's weight and cord clamping practices at delivery.[19,40,56]

A baby born prematurely misses some or all of the iron transfer of the last trimester of pregnancy.[19] Low birth weight babies with smaller organs – the liver and kidneys are iron storage organs – and lower volume of blood have lower total body iron than healthy birth weight babies.[40] The timing of clamping of the umbilical cord after birth is another important factor. Before birth, a baby's circulation includes the placenta, with ~40% of foetal blood in the placenta at any time.[40] Delayed cord clamping allows a higher volume of blood to be transferred from the placenta to the baby. Delayed cord clamping can increase total body iron at birth by 20-33%.[40]

In the first months of life, iron is required for rapid growth and erythropoiesis.[20, 40] The iron content of foetal haemoglobin is high (~170 g/L) for optimal function in the hypoxic intra-uterine environment before birth.[40] During the early months, iron is redistributed from foetal haemoglobin to body stores and back to haemoglobin as the baby grows and blood volume expands.[20] Iron requirements are determined by rate of growth – a rapidly growing baby requires more iron that a baby growing more slowly.[40] In the first months of life, the baby's total body iron at birth is his/her main source of iron, supplemented by a small amount of dietary iron from breastmilk.[20, 40]

A healthy birthweight, breastfed baby, born at term to a well-nourished mother, with the benefit of late cord clamping, is virtually self-sufficient in iron until around age six months.[20] Actual iron intake of breastfed babies is challenging to measure and instead estimates are calculated based on the usual iron content of breastmilk and the estimated volume of breastmilk consumed.[40] Breastmilk provides iron as lactoferrin, another form of iron bound to a chaperone protein. The concentration of iron in breastmilk is low (~0.5 mg/L in early

human milk declining to ~0.35 mg/litre in mature milk) providing ~0.27 mg per day of dietary iron to a baby consuming 750–800 mls of breastmilk.[40] However, lactoferrin is highly absorbed (12% – 56%) depending on the iron status of the infant.[40, 57] The additional iron provided by breastmilk is sufficient to replenish the iron losses from the skin and gut (~0.18 mg/day) of the baby.[40]

Iron requirements of breastfed infants age ~6-11 months; At this age estimated requirements for most nutrient are based on Average Intakes (AIs). However, estimates of daily dietary requirements for iron (and zinc) of healthy babies aged 7-12 months are based on factorial calculations of the iron content of blood and other tissues, adjusted for growth and for losses from the skin and gut. These is sufficient understanding of the factors determining iron requirements in early life to develop an EAR and RDI.[3]

Based on these factorial calculations, a baby needs to accrue about 200 mg of additional iron to supply the needs of expanding blood volume and tissue growth from age 6 months to 12 months.[20] Reflecting this, the requirements for iron of an infant age 7 – 12 months (EAR Iron 7 mg and RDI 11 mg (Figure 1.1) are higher than the requirements of an adult man (EAR 6 mg; RDI 8mg) who no longer needs to accrue iron.[3] Per kilogram of body weight, estimated iron requirements at 6-12 months – 0.9-1.3 mg/kg – are higher than at any other life-stage.[20] These estimates are based on healthy babies - a baby with poor iron status at birth will have higher requirements.[3, 40]

At around age 6 months, babies begin the transition from a totally milk diet to one that includes solid food as well as milk and eventually to a diet that is predominately solid food by around age 2-3 years. Most (98%) of his/her iron must come from solid food.[44]

There are two main constraints on the quantity of complementary solid food that a breastfed baby or young child can consume during this transition; 1) the energy gap between total energy requirements and energy provided by breastmilk 2) the stomach capacity of the child that determines the quantity of solid food the baby/child can consume at any time.

This energy gap has been estimated at ~200 kilocalories (kcals) (837 kilojoules (k'joules)) at 6-8 months, ~300 kcals (1,256 k'joules) at 9-11 months, and ~550 kcals (2,301 k'joules) at

12-23m (1 kilocalories = 4.18 kilojoules).[3,44] The quantity of solid food usually consumed is estimated to be ~137-187g at 6-8 months, ~206-281g at 9-11 months and 378-515g, depending on the energy density of the complementary food.[58]

Because the quantity consumed is small, nutrient density of complementary food will determine if requirements for iron are met in early childhood.[44] Dewey estimates that in terms of nutrient density (mg iron per 100 kcals) compared to requirements of an adult man (0.5 iron mg per 100 kcals), the relative iron requirements of an infant aged 6–8 month are higher by a factor of nine (4.5mg iron per 100 kcals); at 9-11 months (3.0 mg per 100 kcals) higher by a factor of six and at 12 – 23 months (1.0 mg per 100 kcals) twice as high.[44]

Australian guidelines recommend iron-rich complementary foods to meet these high requirements of early life such as lean meat and iron-fortified cereals.[59] A healthy diet for infants aged 6-12 months including iron-fortified infant cereal was modelled in studies conducted in preparation for the 2013 Australian dietary guidelines.[5] However analysis of an example healthy diet consistent with this modelled diet provides 5.83 mg iron; below (83%) the estimated average requirements (EAR 7mg iron) and the RDI (11mg iron; 53%).

Special note

The document referenced here shows the iron content of the modelled diet (p43) to be substantially higher (14.79 mg) than the example diet (6.46mg) analysis by the writer using the Ausnut 2011-13 Food Composition data (Supplementary Table 1.1).[2] The authors will be contacted to clarify the reasons for this difference. [5]

Source: Baghurst el al 2011.[5]

This example diet also exceeds estimates of energy requirements and quantities of food eaten at 6-12 months (Supplementary Table 1.1).

However the high iron requirements of early life can be met with relatively small quantities of traditional foods, because of the higher nutrient density of these foods.[44] Figure 1.2 shows the quantity of several traditional Aboriginal and Torres Strait Islander foods and some introduced foods that would meet iron requirements of infants aged 7-12months.[2, 60]

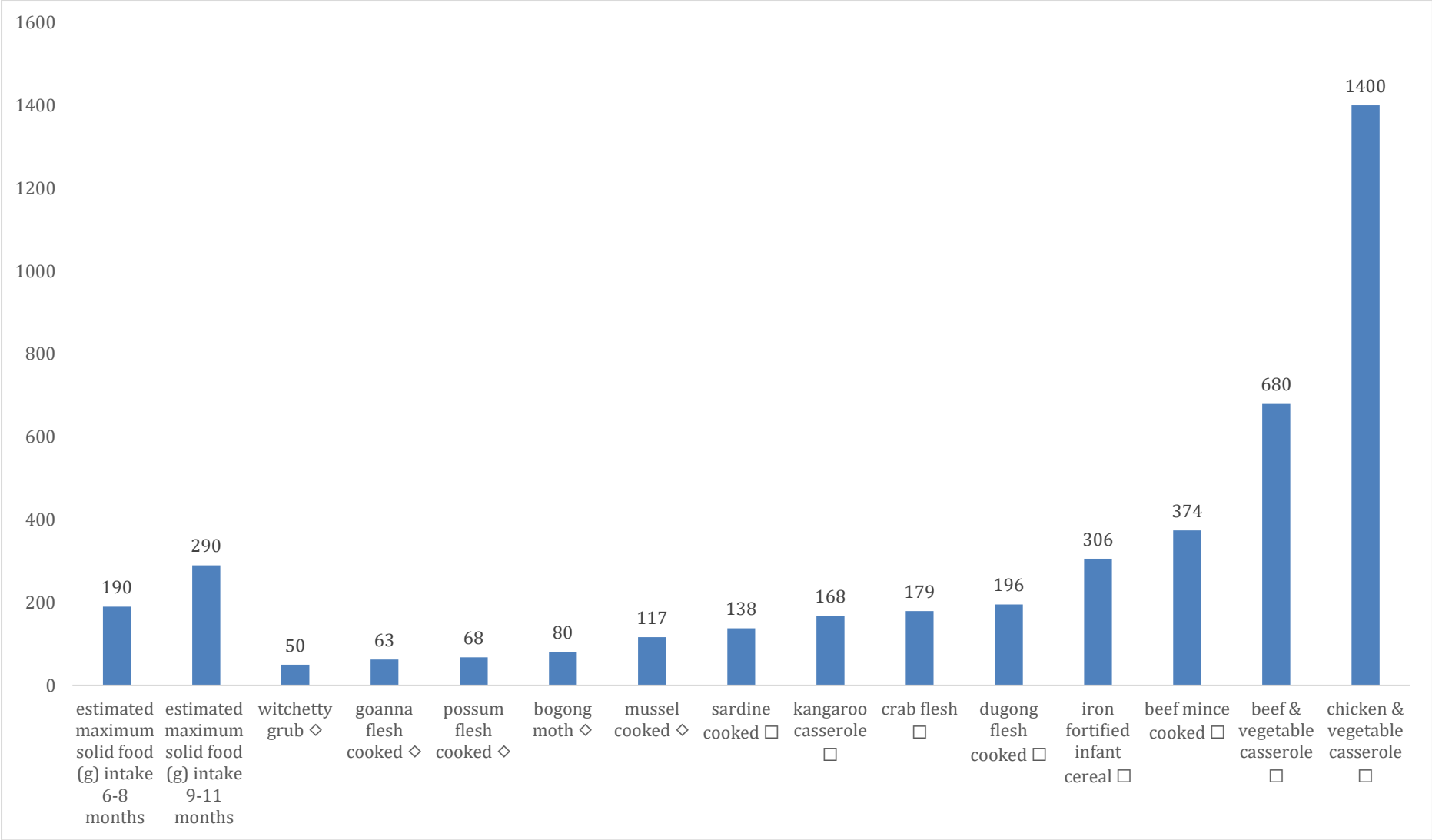

Figure 1.2 Quantity (g) providing Estimated Average Requirement for Iron at 7-12 months (7mg)

Iron requirements of children aged 12-23 months; Meeting iron requirements is more achievable in the second year of life. Requirements are lower due to the slower rate of growth (EAR 4 mg iron per day, RDI 9mg) (Figure 1). Also, children now have increased capacity to eat solid food. Based on the healthy diet model for this age, the iron content of an example healthy diet (4.74mg iron) for young children at age 13-23 months is adequate for children with average requirements (EAR 4mg; 119%) but insufficient for children with higher than average requirements (RDI 9m ; 53%) (Supplementary Table 1.2).[5]

These findings are consistent with studies elsewhere in Australia and New Zealand, which found that young children often consume insufficient meat and other iron-rich food to meet their estimated requirements for iron.[61, 62, 63,64] Meeting iron requirements may be even more challenging for those young children who have poor iron status and/or live on nutrient poor diets.[44]

Dietary Iron in remote Aboriginal and Torres Strait Islander settings; Assessment of dietary intake is challenging in any circumstance.[65, 66] In remote Australia, sales data from community stores and other food outlets have been used to estimate community dietary intake.[67] The use of food sales data as a proxy for dietary intake has limitations; for example information is not available for subsets of the community and sales information does capture any nutrient rich traditional foods that are consumed.[68, 69] However, comparative studies have shown that information on dietary patterns and energy intake obtained by analysis of 2012-13 remote community food-outlet sales data is consistent with self-reported dietary intakes reported by Aboriginal and Torres Strait Islander Australians in the 2012-2013 national health and nutrition surveys.[70]

In one study, changes in remote store purchasing patterns over nearly three decades were examined.[71] Store sales showed increased energy content of purchases with less red meat and sugar sold, and increased sales of convenience foods, take-away foods and sugar sweetened beverages.[71] Overall nutrient density, including iron density, of the purchases declined. Some increases in nutrient density e.g. folate, were attributed to food fortification.[71]

Another study of store sales in three remote communities showed that the iron content of foods and drinks sold (1.5mg per 1000 kilojoules), was more twice the weighed community-

level estimated average requirements (0.72mg iron per 1000 kilojoules per day).[72] However the high iron requirements of early life and the relatively small amounts of solid food consumed, mean that current iron density of store sales is well below requirements in early childhood - less than 30% at age 7-11 months (Supplementary Table 1.3). At 12-23 months, store sales iron density is closer to (~90%) - but still below - requirements (Supplementary Table 1.3).

Analysis of store sales data cannot adjust for variations in diet among the community.[69] Items such as iron-fortified infant cereals are intended only for infants; conversely infants are unable to consume many cuts of meat naturally rich in haem iron, also included in store sales. Overall the reported iron density of current diet, based on store sales may be adequate at a community-level but is insufficient for children aged 6-23 months.

Iron and neurodevelopment; During the first thousand days of life, the brain grows rapidly in size and complexity, reaching ~70% of adult size by age one year and accounting for ~50% of resting energy requirments.[73] Healthy early brain development requires good nutrition, absence of toxic stress and environmental enrichment.[21, 50]

Box 1.2

Neurodevelopment has been defined as; ….*the dynamic interrelationship between environment, genes, and the brain whereby the brain develops across time to establish sensory, motor, cognitive, socioemotional, cultural, and behavioural adaptive functions. [1]*

Source: Bhutta ZA et al 2017[1]

Box 1.2 Definition – Neurodevelopment.

Sufficient iron is needed for haemoglobin to support the high metabolic requirements of the growing brain, and for specific neurodevelopmental processes: neuronal proliferation, axon and dendrite growth, synapse formation, myelination.[50] Neurodevelopment in early life provides the scaffolding for subsequent development.[21] The different regions of the brain (hippocampus, cortex, striatum) and neuro-developmental processes (myelination, neurotransmitters) have different developmental trajectories.[21] While all nutrients are

important, requirements for specific nutrients (protein, long chain polyunsaturated fatty acids (LCPUFAs), iron, zinc, iodine and vitamin B12) increase during critical phases of neurodevelopment.[21, 50]

The effects of any nutrient deficiency will vary with the timing, extent and duration of the deficiency, and with concurrent factors that may exacerbate or moderate any detrimental effects of the deficiency.[21, 50] The specific effects of iron deficiency have been explored in animal studies, mainly using rodent and non-human primate models.[22, 74] These demonstrate the interconnectedness of iron-dependant processes during development with alterations in neurochemistry, neurometabolism, and neuroanatomy , changing central nervous system processes and physiologic regulatory processes.[22, 50, 74] These changes in turn impact on a range of behaviours.[22, 50, 74] In non-human primates the effects of iron deficiency varied with timing; pre-natal iron deficiency resulted in altered activity, impulsivity and wariness, whereas post-natal iron deprivation impaired emotional and cognitive development. [75]

Such animal studies provide information on possible mechanisms but are not necessarily applicable to humans.[76] Current understanding of the effects of iron deficiency on neurodevelopment in human infants is derived from observational and intervention studies. Longitudinal studies in Chile and Costa Rica have shown detrimental effects of iron deficiency in early childhood development, with persistent associations with behavioural indicators in primary school years and adolescence.[74, 77,78]

However there are challenges both in assessing the effect(s) of early childhood anaemia and in assessing whether interventions to improve iron status have benefits in terms of early childhood development.[21]

Nutrient deficiencies, such as iron deficiency, occur in settings of social disadvantage and food insecurity where multiple factors occur that negatively impact of early childhood development.[75] Control of such factors is a key challenge in the design of research studies. [76] Concurrent deficiencies of other nutrients, inflammation and infection, exposure to smoke or heavy metals, poor mother-child attachment associated with poor maternal depression are all factors that impact on child development.[75, 76]

Other issues are those that challenge any longitudinal study; bias due to selective loss to follow-up, inconsistent compliance with the intervention, reverse causality if children who are more attentive and alert are fed a more nutrient-rich diet while children who are more passive who may be perceived as having lower requirements.[76, 79] Another challenge is the subjective nature of assessments of child development, especially difficult in younger children.[76]

An additional challenge in assessing the evidence relates to the methodology used for reviews and meta-analysis of multiple interventions to improve iron status with differences in dosage, timing, duration and different outcome measures.[21] A finding of nil effects may be due to methodologic differences in the various studies included, not to a true absence of effect.[21]

One example relates to the timing of interventions as detrimental effects of deficiencies of key nutrient(s) during a critical phase of neurodevelopment may not be rectified by subsequent provision of adequate amounts of the nutrient(s).[21, 50] However, increased mental development scores among infants with iron deficiency anaemia in response to parental treatment with iron demonstrates that postnatal treatment can be effective in infancy.[80]

One recent review found no evidence of benefit in child developmental indicators from interventions to improve iron status of mothers during pregnancy or pre-school aged children but did find evidence of benefit among anaemic school-age children.[76] This review discussed various possible reasons for these findings including a) that the interventions had nil effect; b) that developmental indicators are more challenging to assess in younger children compared to school-age children; or c) differences in the intervention methodologies. The review authors highlight the need for high quality, placebo controlled, adequately powered randomised control trials to assess the effect of iron interventions on cognitive performance in young children.[76]

Assessing early childhood development at school age in Australia; The Australian Early Development Census (AEDC) is a national census of early childhood development, conducted every three years since 2009.[81] Each child in the first year of full time school is assessed by his/her teacher on five domains of early childhood development; physical

health and wellbeing, social competence, emotional maturity, language and cognitive skills (school-based), communication skills and general knowledge.[81] These AEDC domains are predictive of outcomes in health, well-being and academic success in later life.[82]

AEDC has developed categories of developmental status (on track, developmentally at risk, developmentally vulnerable) based on the first AEDC in 2009.[81] Children scoring below the AEDC 2009 tenth centile for each domain are categorised as developmentally vulnerable for that domain. Children with scores below the tenth centile for one or more of the five AEDC domains are categorised as DV1. Children with scores below the tenth centile for two or more domains are categorised as DV2.[81] In Australia, AEDC results have been shown to predict subsequent National Assessment of Performance Literacy and Numeracy (NAPLAN) scores for numeracy and reading.[83]

Initially developed in Canada and adapted subsequently for use in Australia and elsewhere, concerns have been raised about the appropriateness of the AEDC instrument in Australian Aboriginal and Torres Strait Islander settings.[84] Research undertaken in 2008-09 in urban, regional and remote Western Australia provided the basis of an adaption of the AEDC methodology so that teachers are supported by Indigenous cultural consultants during the assessment of childhood development of Aboriginal and Torres Strait Islander children.[84] One strength of the AEDC information is that the information provided encompasses all children in Australia from diverse cultural and linguistic groups including Aboriginal and Torres Strait Islander children.[81]

The 2018 AEDC census with 308,953 child participants with an average age of 5 years 7 months found that 21.7% were developmentally vulnerable – scoring below the tenth centile - on one or more domains (DV1) and 11.0% developmentally vulnerable on two or more domains (DV2).[81] More boys were developmentally vulnerable than girls.[81]

Australian studies have shown that early disadvantage as reflected in perinatal factors - low birth weight, prematurity - and lower socio-economic status of families is associated with increased risk of AEDC development vulnerability at school age among both Aboriginal and non-Aboriginal children.[85,86]

Iron and growth. Iron deficiency with or without anaemia is most prevalent in situations where poverty and food insecurity means that poor nutrition, high rates of infections and poor growth in early life are common.[11,4,6] However, despite this frequent co-occurrence, poor growth and early childhood anaemia appear to have different aetiologies.[87,88] This is demonstrated by the occurrence of iron deficiency in settings where childhood growth is not impaired.[11] Another indication of different aetiology is that children who grow most rapidly are at higher risk of iron deficiency and anaemia that children who grow more slowly.[20] Children under age two years have higher iron requirements- and more anaemia - than older children who have slower rates of growth.[89] Children who were low birth weight and/or premature are at higher risk of iron deficiency and anaemia compared to other children; these babies typically have lower iron stores at birth than full-term, healthy birthweight babies, and may exhibit rapid 'catch-up' growth in early life.[20] Babies born to mothers with diabetes in pregnancy often experience rapid in-utero growth, and are at higher risk of iron deficiency.[90] A further indication of different aetiologies is that interventions that are effective in prevention and/or treatment of early childhood anaemia may have little effect on growth.[91,92]

These findings are consistent with the theory of 'growth nutrients or 'type two nutrients' - a group of nutrients including protein, energy, zinc, copper, potassium, magnesium; all of which are required in adequate amounts for growth.[93, 94] A deficiency of one or more growth nutrients will result in poor growth. Other nutrients - iron, iodine, thiamine and vitamin A - are categorised as 'type one' nutrients where a deficiency will result in a specific nutrient deficiency condition without initial impact on growth.[93, 94] Conversely, it has been reported that high iron intake in early life because of excessive supplementation or fortification of infant formula, may be associated with poor linear growth possibly associated with reduced absorption of other micronutrients such as zinc – a 'growth nutrient' - in the presence of high gastro-intestinal levels of iron.[20]

Iron and infections; Infections and nutrition status have a bidirectional relationship.[95] Iron deficiency is prevalent in settings where the burden of infection is high.[11] Infections suppress appetite so frequent infections can have a negative effect on nutrition status and growth in early childhood.[95] Conversely a poorly nourished child is more susceptible to infections.[95] Infections that commonly cause iron deficiency and/or anaemia include

hookworms and malaria.[95] The resultant iron deficiency remains after the infection has passed. Poor nutrition and infection can each cause iron deficiency but these are not mutually exclusive causes. Prevention of infections will complement nutrition-focused interventions to prevent iron deficiency and iron deficiency anaemia.[15]

Infections can cause iron deficiency and conversely, high doses of iron for treatment or prevention of iron deficiency can promote infections.[47, 52] Non-physiological doses of iron can overwhelm the body homeostatic systems which tightly control iron absorption and limit un-chaperoned forms of iron, thus increasing the available iron for pathogens.[47] This effect is a particular concern in settings where malaria and tuberculosis are endemic , especially for children before age nine months whose iron homeostasis systems are still immature.[47, 111] Food fortification with the lower doses of iron provided in a food matrix appears to be a safer option.[52]

Iron and immunity; The inter-relationship of iron status and infections is complicated by the acute phase immune response to infections.[96] During any infection, the host is the source of nutrients that pathogens require to thrive.[96] Iron is important not only in human metabolism but in the metabolism of virtually all bacteria and protozoa.[52, 96] The exceptions to this include some bacteria recognised as benign to the human host - Bifidobacteriaceae and Lactobacilli - common in gut and vaginal microbiome.[52]

Most host nutrients are readily available to pathogens but the innate immune response to infection 'starves the invaders' sequestering iron to make iron unavailable to pathogens.[96] The immune response, mediated by the peptide hepcidin, triggers alterations in levels of several chaperoned forms of iron; ferritin levels rise while transferrin levels drop.[97] While this immune response protects against infections, iron becomes unavailable for normal metabolic processes, such as erythropoiesis. When the infection is repeated or persistent, these immune processes can lead to iron-restricted anaemia.[96, 97] The same immune response can be triggered by metabolic inflammation associated with chronic disease.[97]

Conversely high levels of non-chaperoned iron available to pathogens, may promote infections.[47] It has been suggested that genetically inherited haemoglobinopathies such as sickle cell disease and the thalassaemias, developed because the resultant anaemia provided protection against infections such as malaria, and thus a survival advantage.[11]

Increased understanding of the negative effects of high doses of iron has prompted debate about the appropriate level of iron fortification of infant formulas.[57, 111] In the first months of life, an exclusively breastfed baby will usually thrive on the low-iron diet provided by breastmilk.[57] The resultant low-iron environment of the gut of the breastfed baby is an environment where organisms which do not utilise iron - Bifidobacteriaceae and Lactobacilli - can also thrive.[42, 52, 57] Infant formulas fortified with higher content of poorly absorbed iron (4-12mg iron/L) may increase available iron in the infant gut, potentially altering the normal infant microbiome.[57 52] The potential effects of this high iron environment in the infant gut on the infant microbiome, gut integrity and developing immune system are not yet clearly understood.[52, 57, 111] By contrast, breastfeeding protects against infections and has particular benefits for healthy neurodevelopment.[42]

Metabolic exclusion of iron may be as important as securing sufficient iron for health, a factor that needs to be considered in developing safe interventions to address iron deficiency.[47, 52] Current research is exploring the incorporation of measures of hepcidin levels into other measures to assess iron status, in order to identify individuals who may safely be provided with iron supplements.[47, 52,98]

Differentiating the causes of anaemia; The terms anaemia, iron deficiency anaemia and iron deficiency are often used interchangeability, reflecting an erroneous assumption that all anaemia is due to iron deficiency.[11] However anaemia – defined by low haemoglobin levels - has various causes as described above; genetic conditions, chronic inflammation, blood loss associated with a range of medical conditions are other non-nutritional causes of anaemia.[99] As well as iron deficiency, other nutritional deficiencies – folate, vitamin B12 – can cause anaemia.[11, 99]

Differential diagnosis of the cause(s) of anaemia requires full blood counts and other laboratory investigation.[11] Deficiencies of folate and vitamin B12 can be distinguished from iron deficiency as by differences in red blood cell size; red blood cells are larger than normal – macrocytic – in folate and vitamin B12 deficiency, and smaller – microcytic - in iron deficiency.[11] Studies published in 1986 and 1991 reported that many remote community residents (15% up to 70%, varying between communities) in northern Australia had folate deficiency.[100] However since fortification of bread flour was made mandatory in 2009, low

folate levels are now rare among Aboriginal and Torres Strait Islander people.[101, 102] Vitamin B12 has not been identified as a cause of anaemia among Australian Aboriginal and Torres Strait Islander people. [100] Thalassaemia traits have been assessed in three coastal settings, with findings ranging from nil to 2.7% to 27% of residents with those traits.[100]

Assessing iron status; Iron status can be assessed by various measures including levels of iron in different chaperoned forms; ferritin - the storage form of iron; transferrin - the form of iron transported between cells; and transferrin saturation.[18, 16] Assessment of iron status is further complicated by infections and by inflammation, due to changes in levels of ferritin and transferrin. A recent series of studies – the BRINDA project (Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia) – investigated strategies to assess iron status and Vitamin A status in low-infection and high-infections setting.[15] BRINDA recommendations are to include measures of metabolic markers of inflammation (C-reactive protein and alpha-1-acid glycoprotein) to assist interpretation of levels of ferritin to assess iron status. [15]

Other indicators of iron status include mean corpuscular volume (MCV) an indicator of average size of red blood cells; reticulocyte haemoglobin content (CHr) an indicator of iron availability for erythropoiesis; and erythrocyte zinc protoporphyrin (ZPP) an indicator of haemoglobin production.[16, 18] Each of these measures provides information on different aspects of iron homeostasis and/or erythropoiesis.[18] Some may be altered in the presence of other conditions – for low values of MCV indicate late stage iron deficiency but can also be due to thalassemia.[16] Multiple indicators may be required to assess iron status to interpret results, given the varying effects of other conditions – thalassaemia, inflammation - on these indicators.[15]

The BRINDA group found that when levels of ferritin were adjusted for inflammation , iron deficiency was the main contributing cause of anaemia among women and young children where the burden of infection is low, but also a consistent contributing cause of anaemia to varying degrees in high-infection settings.[103, 104]Research into the effects of anaemia commonly define iron deficiency anaemia as one or more abnormal haemolytic measures of iron status together with low haemoglobin.[105]

Apart from technical challenges in iron status assessment, a further challenge is the cost of measuring these indicators.[106] Only ZPP can be measured outside of a laboratory.[16] Assessment of other indictors is complex, requiring separation of serum and plasma, specialised laboratory analysers and time. The high cost of these tests precludes iron studies as part of routine child health checks.[106] In addition, the requirement for venous blood for these tests that is rarely acceptable to parents and carers of babies and young children.[106]

A further issue is important in assessing the association of iron deficiency and/or anaemia with neurodevelopment. Haematological markers of iron status do not necessarily reflect availability of iron in the brain.[18,17] As yet no indicators of iron status provide information on the availability of iron for the many iron-dependant processes required for healthy neurodevelopment. [17, 21]

By contrast with indicators of iron status, haemoglobin can be measured at low cost using a point-of-service device but measurement of haemoglobin as an indicator of iron deficiency is neither sensitive nor specific. [16, 18] Low iron status and iron deficiency precede the onset of iron deficiency anaemia so Iron deficiency may be present when haemoglobin levels are in the normal range. [21] Conversely erythropoiesis may slow and haemoglobin levels drop in the present of infections despite adequate iron stores, resulting in 'iron restricted' anaemia.[97]

Other issues relate to the use of capillary blood for point-of-service devices as capillary blood has lower levels of haemoglobin compared to venous blood, a factor that may result in over-diagnosis of anaemia.[107, 11] Poor skill of operators may also result in lower levels of haemoglobin and false positives in diagnosis of anaemia. The reliability of these devices is enhanced when staff are well trained and skilled in their use.[11]

Assessment of haemoglobin levels in young children using capillary blood and point-of-service devices is routine health service practice in remote Australian communities.[12,13,14] Treatment protocols are based on a premise that anaemia is usually due to iron deficiency. Children with anaemia are treated with iron (30-60mg iron per day for 1-3 months depending on age/weight of child) and anti-helminths.[13,14, 12] Additional investigation is recommended only where haemoglobin is less than 9 mg/L or if there is poor response to iron treatment.[12, 13, 108]

Coverage of young Aboriginal and Torres Strait Islander children by these health service protocols varies in different settings across northern Australia, ranging from, 70.2% of children (n = 2096) in Western Australia, 72.1% of ECNAPP participant children (n = 262) to 85% of children with a health record (n = 398) in two remote Northern Territory communities.[29,30, 109]

These coverage figures indicate possible selection bias in recorded information on child haemoglobin measurements if health staff are less likely measure haemoglobin levels of some children – perhaps those perceived as 'more healthy' or those who do not present for routine checks.[79] Routine antenatal care coverage for pregnant mothers appears higher, albeit still incomplete. In the Northern Territory communities where 93% (n = 384) of mothers had a record of at least one antenatal care visit and 91% (n = 348) had blood examinations and haemoglobin measurements recorded.[31]

Two studies show the association of iron deficiency with childhood anaemia in remote Northern Territory community settings. Among pre-school-aged Aboriginal children (n = 74) with anaemia, measures of iron status showed that most (n = 62, 83.8%) had iron deficiency anaemia, with folate deficiency and chronic infections identified as other causes of anaemia.[8] Among school-age children with anaemia (n = 201) in a similar setting, iron therapy was effective in resolving anaemia among 83% of the 66 children for whom follow-up measurements were available.[110] Haematological studies among people over age five years in remote community settings in northern Australia found that iron deficiency was the most common cause of anaemia in those communities.[100]

1.3 Discussion

Anaemia in early life is prevalent in Aboriginal and Torres Strait Islander settings across northern Australia. The evidence presented here points to iron deficiency as the 'usual suspect' causing anaemia in early childhood Aboriginal and Torres Strait Islander children due to the combination of high iron requirements and the challenges of achieving sufficient dietary iron intake in pregnancy and early life.

Babies at higher risk of iron deficiency are those who were born to mothers with poor iron status, and/or born prematurely and/or low birth weight. Despite recent improvements,

these factors are more common among the babies of Aboriginal and Torres Strait Islander mothers compared to other Australian babies.[112] In addition, their mothers are more likely to be disadvantaged in terms of socio-economic status compared to other Australian mothers, and consequently the cost of a nutrient-rich healthy diet is even more challenging , especially for those living with the high cost of healthy food in remote Australia.[34, 112]

Breastfeeding offers neurological benefits for all babies but is of particular benefit to low birth weight and premature babies.[42] It is important that any intervention to reduce early childhood anaemia includes strategies to promote, support and protect breastfeeding.[113] The breastfed baby requires nutritious food from around age 6 months to complement breastmilk; this solid food is the main source of iron at a time when requirements are higher than at any other life-stage.[20] But healthy food given to complement breastfeeding, even with the inclusion of iron fortified cereals, may not provide sufficient iron to meet the needs of babies at 6-11 months, especially those with iron requirements at the high end of the normal range. Children aged 12-23 months may also be unable to meet their iron requirements from healthy food alone, more so if their diet is nutrient-poor and/or their iron status compromised.[44]

Health service protocols for treatment of early childhood anaemia in northern Australia reflect an understanding that this anaemia is caused by iron deficiency. However, subsequent treatment of anaemia may not reverse any neurodevelopment disadvantage.[20, 21, 50] Anaemia due to iron deficiency is a late stage of iron deficiency; the rapid neurodevelopment of early life may be compromised by iron deficiency before anaemia develops.[20, 21, 50] Interventions that are initiated once anaemia is diagnosed will not benefit babies and young children who are iron deficient but not yet anaemic.

Prevention of anaemia in the first one thousand days of life is an opportunity to enhance early cognitive development and to support Aboriginal and Torres Strait Islander children to develop to their full potential.[21] The under-pinning purpose of this research to provide information to the Aboriginal and Torres Strait Islander peoples of Far North Queensland about the issue of anaemia in the first thousand days of life in the remote communities, together with information about options for effective interventions.

1.4 Thesis Aim and Objectives

This PhD was undertaken with the aim of investigating anaemia among Aboriginal and Torres Strait Islander children and their mothers in Far North Queensland; objectives of the study were to:

- Describe anaemia in pregnancy and the risk factors for anaemia in pregnancy among mothers
- Describe anaemia in early childhood – anaemia at age 6-23 months – and the risk factors for early childhood anaemia
- Describe the association between early childhood anaemia and child development assessed in the first year of full -time school
- Review interventions for effectiveness in the prevention of early childhood anaemia

Supplementary Table 1.1

Food composition analysis of example modelled diet for infant aged 6-12months (Ausnut 2011-13 Food Composition database[2]).

Ausnut Food ID	food.	energy KJ per 100g	Iron mg per 100g	weekly quantity g	weekly energy content kj	weekly iron content mg	daily quantity g/ml	daily energy content kj	daily iron content mg
13A11834	sweet potato, steamed	319	0.51	20	63.8	0.102	2.86	9.11	0.01
13A11753	potato, steamed	280	0.5	20	56	0.1	2.86	8.00	0.01
13A11885	broccoli, steamed	114	0.7	30	34.2	0.21	4.29	4.89	0.03
13A11887	cabbage, steamed	93	0.59	30	27.9	0.177	4.29	3.99	0.03
13A11816	carrot, steamed	129	0.28	30	38.7	0.084	4.29	5.53	0.01
13A12537	pumpkin, steamed	294	0.19	30	88.2	0.06	4.29	12.60	0.01
13A11727	peas, steamed	246	1.1	30	73.8	0.33	4.29	10.54	0.05
13A11739	tomato	74	0.27	30	22.2	0.081	4.29	3.17	0.01
13A20126	red kidney beans steamed	441	2.1	20	88.2	0.42	2.86	12.60	0.06
06B10090	orange, peeled, raw	178	0.39	30	53.4	0.117	4.29	7.63	0.02
06D10518	banana, peeled, raw	474	0.4	30	142.2	0.12	4.29	20.31	0.02
02B10603	bread, white	993	1.48	200	1986	2.96	28.57	283.71	0.42
02B10679	bread, white & wholemeal	1063	1.71	200	2126	3.42	28.57	303.71	0.49
08C10432	chicken breast roasted, nil fat	637	0.5	60	382.2	0.3	8.57	54.60	0.04
08A11143	beef mince stewed	963	1.83	120	1155.6	2.196	17.14	165.09	0.31
09B20083	cheese, cheddar	1611	0.15	10	161.1	0.015	1.43	23.01	0.00
09C10098	yoghurt, natural	309	0.07	40	123.6	0.028	5.71	17.66	0.00
04B10077	margarine spread, polyunsaturated	2552	0	35	893.2	0	5.00	127.60	0.00
07B10086	infant cereal, + iron & vitC, dry	1636	20.6	140	2290.4	28.84	20.00	327.20	4.12
09A10228	breastmilk , mature	286	0.03	4200	12012	1.26	600.00	1716.00	0.18
							Total	3,167 kj	5.83 mg

Solid food (including 180g infant cereal ready-to-eat); weight = 318g, energy content = 1401 k'joules/335 k'cals Total diet iron 5.83 mg (7- 12m EAR 7mg, RDI 11mg) = 83% EAR, 53% RDI.

[2] source Food Standards Australia New Zealand. Ausnut 2011-13 http://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/Pages/default.aspx2014

Supplementary Table 1.2

Food composition analysis of modelled diet for children aged 13–23 months (Ausnut 2011-13 Food Composition database [3]).

Ausnut Food ID	food	energy KJ per 100g	Iron mg per 100g	weekly quantity g	weekly energy content kj	weekly iron content mg	daily quantity g/ml	daily energy content kj	daily iron content mg
13A11834	sweet potato, steamed	319	0.51	93.75	299.0625	0.478125	13.39	42.72	0.07
13A11753	potato, steamed	280	0.5	93.75	262.5	0.46875	13.39	37.50	0.07
13A11885	broccoli, steamed	114	0.7	131.25	149.625	0.91875	18.75	21.38	0.13
13A11887	cabbage, steamed	93	0.59	131.25	122.0625	0.774375	18.75	17.44	0.11
13A11816	carrot, steamed	129	0.28	131.25	169.3125	0.3675	18.75	24.19	0.05
13A12537	pumpkin, steamed	294	0.19	131.25	385.875	0.25	18.75	55.13	0.04
13A11727	peas, steamed	246	1.1	262.5	645.75	2.8875	37.50	92.25	0.41
13A11739	tomato	74	0.27	262.5	194.25	0.70875	37.50	27.75	0.10
13A20126	red kidney beans steamed	441	2.1	75	330.75	1.575	10.71	47.25	0.23
06B10090	orange, peeled, raw	178	0.39	262.5	467.25	1.02375	37.50	66.75	0.15
06D10518	banana, peeled, raw	474	0.4	262.5	1244.25	1.05	37.50	177.75	0.15
02B10603	bread, white	993	1.48	340	3376.2	5.032	48.57	482.31	0.72
02B10679	bread, white & wholemeal	1063	1.71	640	6803.2	10.944	91.43	971.89	1.56
08C10432	chicken breast roasted, nil fat	637	0.5	227.5	1449.175	1.1375	32.50	207.03	0.16
08A11143	beef mince stewed	963	1.83	227.5	2190.825	4.16325	32.50	312.98	0.59
09B20083	cheese, cheddar	1611	0.15	500	8055	0.75	71.43	1150.71	0.11
09C10098	yoghurt, natural	309	0.07	500	1545	0.35	71.43	220.71	0.05
04B10077	margarine spread, polyunsaturated	2552	0	35	893.2	0	5.00	127.60	0.00
09A10228	breastmilk, mature	286	0.03	1000	2860	0.3	142.86	408.57	0.04
							Totals	4,083	4.74

Total quantity solids 473g; total diet energy content including breastmilk 4,083 kjoules/878 kcalories
Iron content total diet 13-23m = 4.74mg (12-23m EAR 4mg, RDI 9mg) 119% EAR, 53% RDI.
Iron content total diet 13-23m = 8.27mg (12-23m EAR 4mg, RDI 9mg) 206% EAR, 92% RDI

[3] source Food Standards Australia New Zealand. Ausnut 2011-13 http://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/Pages/default.aspx2014

Supplementary Table 1.3

Estimated proportion of Iron requirements (mg/1000 kilojoules) of children 6-23 months provided by current remote store food and beverage sales.[4]

Child's age	Current estimated iron density (mg/1000 k'joules) remote store food & beverage sales[72]	Estimated energy requirements to be met by solid food (k'joules per day)[58]	Estimated iron requirements to be met by solid food (98% of EAR)[58] (mg per day)	Estimated required iron density (mg iron per 1000 k'joules)	Proportion iron requirements met by current iron content of store food/beverages sales
7-8 months	1.5	836.8	6.86	8.2	18.3%
9-11 months	1.5	1255.6	6.86	5.5	27.3%
12 - 23 months	1.5	2301.1	3.92	1.7	88.2%

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Foreword Chapter 2 (Methods)

In Chapter 1, I described the rationale for this research and the 'metabolic context' in which iron deficiency can develop in the first thousand days of life. In Chapter 2, I describe the study context, the methods used for this study and the information secured through data linkage that was the basis of the subsequent research; information was obtained for two cohorts of Aboriginal and/or Torres Strait Islander mothers and children, where the children were born between 2006 and 2010.

Figure 2.1 Map 1 shows the geographical scope of this research. Four of the five data collections accessed for this research hold information from across the Far North Queensland region, while the fifth data collection, Ferret, is used mainly by community health services for the remote Aboriginal and Torres Strait Islander communities of Far North Queensland. The thirty-eight remote localities using the Ferret system are marked on Figure 2.1 Map 1.

The information presented in this chapter was published in the *Australian and New Zealand Journal of Public Health* in October 2018;

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Chapter 2 Linking 'Data Silos' to Investigate Anaemia Among Aboriginal and Torres Strait Islander Mothers and Children in Far North Queensland

Table 2.1
List of Tables in article Linking 'data silos' to investigate anaemia among Aboriginal and Torres Strait Islander mothers and children in Far North Queensland.

Table 2.2
List of Figures in article Linking 'data silos' to investigate anaemia among Aboriginal and Torres Strait Islander mothers and children in Far North Queensland.

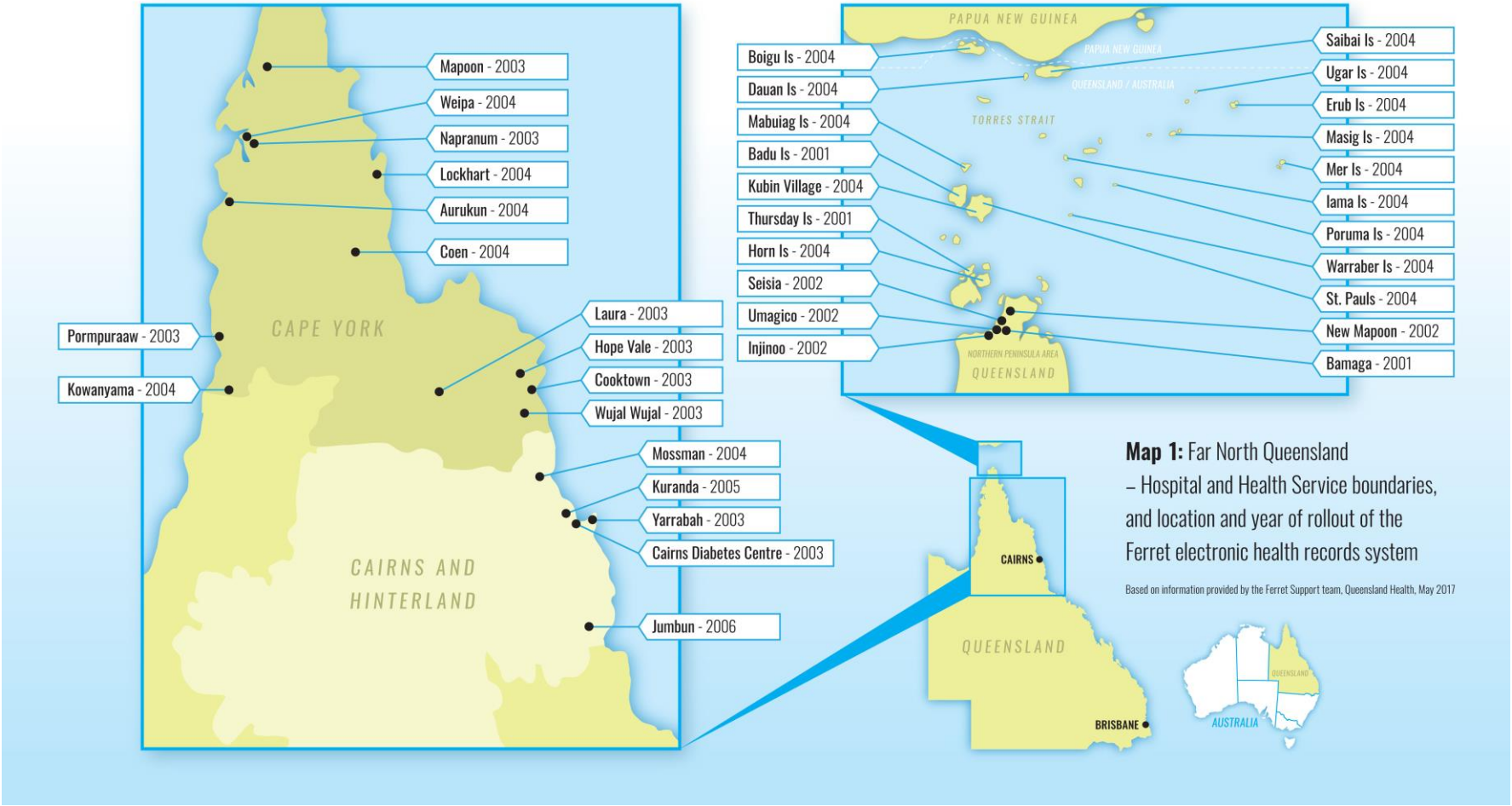

Figure 2.1 Map 1: Far North Queensland Hospital and Health Services boundaries, and location and year of rollout of the Ferret electronic health records system.
(Source: Melissa Parker, Conceptual Graphic Design)

2.1 Article: Linking 'Data Silos' to Investigate Anaemia Among Aboriginal and Torres Strait Islander Mothers and Children in Far North Queensland

Linking 'data silos' to investigate anaemia among Aboriginal and Torres Strait Islander mothers and children in Far North Queensland

Dympna Leonard,[1] Petra Buettner,[1] Fintan Thompson,[1] Maria Makrides,[2] Robyn McDermott[1]

Abstract

Objective: Data collection 'silos' can be linked for health research. Anaemia in early childhood is a long-recognised health issue in remote Aboriginal communities of the Northern Territory and Western Australia, but information is lacking for Queensland. The objective of this work was to compile existing information from health and education data collections to investigate anaemia among Aboriginal and Torres Strait Islander mothers and their children in Far North Queensland.

Methods: Data mapping identified four health data collections and one education data collection holding relevant information. Data Custodians' approval was secured for release of linked de-identified information.

Results: Approval processes and preparation of the dataset for release took 23 months. Birth information was obtained for 2,205 mother–child pairs where the Aboriginal and/or Torres Strait Islander child was born in Far North Queensland between 2006 and 2010. Pathology information from before/during pregnancy was obtained for 2,126 mothers (96.4%), growth and haemoglobin information for 982 children (44.5%), and childhood development indicators at school entry for 963 children (43.7%).

Conclusion: Linking existing information 'silos' enables research into key public health issues.

Implications for public health: Information linkage is particularly valuable in respect of vulnerable populations including rural and remote Aboriginal and Torres Strait Islander peoples.

Key words: linkage, anaemia, Indigenous, mothers, children

Centralised data collections are potentially rich resources for public health research; however, their value is limited if the data is held in isolation from other relevant information sources.[1] The term 'data silos' has been used to describe such isolated data collections.[2] Linkage of data silos for longitudinal and intergenerational research can have particular advantages in respect of time and cost.[1,2] Here, we describe the process and results of our work to access and link existing data collections to investigate anaemia among Aboriginal and Torres Strait Islander mothers and their children in Far North Queensland.

Anaemia is a long-recognised problem among Aboriginal and Torres Strait Islander pre-school and school-aged children of remote communities in the Northern Territory and Western Australia.[3-7] Recent reports indicate that anaemia in pregnancy is also prevalent.[8] In remote Far North Queensland, most of the population (n=14,107 [71.5%]) is made up of Aboriginal and Torres Strait Islander people.[9] Similar issues with anaemia might be expected; however, there is currently no information to clarify the situation.

Anaemia is defined as low blood haemoglobin levels, measured in grams per litre (g/L). Cut-offs vary by age, sex and life stage and may be further adjusted for smoking and for locations at high altitude. The World Health Organization recommended cut-offs are the most commonly used (six months up to five years <110 g/L; 5–11years <115 g/L; 12–14 years <120 g/L; non-pregnant women 15 years and older <120g/L; pregnant women <110g/L, men 15 years and older <130 g/L).[10]

In many countries, including affluent countries such as Canada, the United States and Australia, anaemia is higher among the Indigenous populations compared with the general population.[11] This was shown in the recent Australian national health survey that identified participants who were at risk of anaemia.[12] Among Australian Aboriginal and Torres Strait Islander adults, 7.6% were at risk of anaemia, which is almost double the prevalence (4.5%) among non-Indigenous Australians (age adjusted rate ratio 1.9). More Australian Aboriginal and Torres Strait Islander women compared to men (10.3% vs. 4.8%) were at risk of anaemia and more Aboriginal and Torres Strait Islander people in remote compared to non-remote locations (10.1% vs. 6.9%).[12,13]

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The higher prevalence of anaemia among Aboriginal and Torres Strait Islander Australians is consistent with the lower socioeconomic status of Aboriginal and Torres Strait Islander people compared with other Australians.[14] Among all Australians, the risk of anaemia increases with lower incomes, and is higher among women than among men.[15]

Infection, inflammation and genetic conditions can cause anaemia.[16] However, deficiencies of iron and/or other nutrients remain the most common cause of anaemia among women and young children worldwide.[17] In the Northern Territory, the positive response to treatment with iron supplements for anaemic pre-school-aged and school-aged children indicates that iron deficiency is the cause of childhood anaemia in that setting.[7,18]

In early life, the principal source of iron for the rapidly growing infant is not breastmilk or infant formula but the iron endowed to the child by the mother, mostly during the last ten weeks of pregnancy.[19] Anaemia of a mother in pregnancy is strongly associated with early onset anaemia of her child.[20] For reasons that are not yet clear, maternal diabetes in pregnancy is also associated with early onset anaemia in the child.[21]

Anaemia has negative effects on the health of pregnant mothers, ranging from increased fatigue to increased risk of post-partum haemorrhage.[22] These effects, however, vary depending on the stage of gestation and severity of anaemia. Excessively high haemoglobin levels are also associated with poor pregnancy outcomes.[23] In young children, anaemia can compromise both health and development.[24,25] Anaemia in early childhood may have long-term negative effects, with lower levels of educational attainment during school years.[26,27] These detrimental effects can persist even when anaemia has been treated. Consequently, effective prevention of anaemia is important, especially in the first 1,000 days of life – through pregnancy to around two years of age – when growth and development are most rapid.[24,28]

The work described here has created linked records for mother–baby pairs from before pregnancy, through pregnancy, from birth, and through early childhood up to school entry using existing data collections. These linked intergenerational longitudinal records will be used to investigate anaemia among Aboriginal and Torres Strait Islander children and their mothers in Far North Queensland. This report describes the methods used to secure this information and the resultant data collection.

Methods

An overview of the planned research and the associated key variables by life-stage is shown in Table 1. Four Queensland Health data collections and the Department of Education Australian Early Development Census were identified as information sources. The key variables were identified from each respective data dictionary and listed in ethics and public health act applications.

Details of these five data collections are shown in Supplementary Table 1. Four are centralised whole-of-population data collections while one – Ferret (Ferret, Pen Computer Systems) – is used mainly in remote Far North Queensland.[29,30] The 38 localities using Ferret and the year when the Ferret system was rolled out are shown in Figure 1.

Scope

The geographic reach is Far North Queensland (Figure 1). The information was collected over 15 years, from 2000 to the end of 2015.

Study design and participants

The planned research will be a retrospective cohort study. Information was sought for two cohorts of Aboriginal and Torres Strait Islander mothers and their children.

The Cape York Child Growth cohort included Aboriginal and/or Torres Strait Islander children of the remote communities of Cape York, born between January 2006 and December 2008, and their mothers. These children were a subset of children included in previous unpublished health service research, born after the introduction of Ferret in the Cape York remote communities.

The 2009 and 2010 birth cohort included children and their mothers, where the child was born to an Aboriginal and/or Torres Strait Islander mother in Far North Queensland in 2009 or 2010.

Ethics and related approvals

Ethics approval granted by the Queensland Health Cairns and Hinterland Human Research Ethics Committee included a waiver of the requirement for participant consent to use their information. Details and timeframe for the subsequent Queensland Public Health Act approval processes are shown in Supplementary Table 2.

Data linkage

Once the required approvals had been secured, the requested information was extracted and provided to the Queensland Health data linkage team by the respective Data Custodians. The data linkage team created linkage keys for each mother and baby/child. Two of the four health service data collections (the Perinatal Data Collection and the Queensland Hospitals Admitted Patients Data Collection) are linked on an ongoing basis in a Master Linkage File that was accessed for this research.[30] The data linkage team used Linkage*Wiz* (Linkage*Wiz* v5.5.42 2015 Linkage*Wiz*Software http://www.linkagewiz.net/index.htm) for probabilistic linking of information from the three other data collections. Manual clerical review was also undertaken where required.[30]

Table 1: Sequence of life stage, key variables and data collection sources for each mother and baby pair required for planned research to investigate anaemia among Aboriginal and Torres Strait Islander mothers and their babies in Far North Queensland.

Life stages:	Mother (this pregnancy and prior) →	Baby at birth →	Child: birth to age 5 years →	Child: first year of school
Key variables	Ethnicity, location usual residence, parity/age at birth of cohort baby, anaemia in pregnancy, gestational diabetes, pregnancy inducted hypertension, pathology test results, height and weight, smoking, diet	Sex, gestational age, weight, length and head circumference at birth, APGAR 1&5, hospital admissions, length of stay, discharge status and ICD codes, initial infant feeding	Sequential measurements of weight, length/height and haemoglobin, early childhood development milestones (Y/N), hospitals admissions, length of stay, discharge status and ICD codes	Developmental Index for each of 5 domains: physical health and well being, social competence, emotional maturity, language and cognitive skills, communication skills and general knowledge. Developmental Categories: on track, at risk, vulnerable
Data sources	Auslab, Perinatal Data Collection (PDC)	Perinatal Data Collection (PDC), Queensland Hospitals Admitted Patients Data Collection (QHAPDC)	Ferret, Queensland Hospitals Admitted Patients Data Collection (QHAPDC)	Australian Early Development Census (AEDC)

Linkage files were given sequentially to the researchers as data became available and the final complete linkage file was provided in May 2017. The researchers used the given linkage keys to merge the information from the five data collections for each mother–child pair.

Assessment of data quality and of selection bias

For this report, data quality was assessed by considering the proportion of missing data and implausible values. Comparisons with census information on population numbers and ethnicity were made to assess data completeness and possible selection bias.

An additional comparison was made in respect of mothers and newborns of the 2009 and 2010 birth cohort. These mothers and babies came from both remote and non-remote localities in Far North Queensland. All of these babies had a record on the Perinatal Data Collection (PDC) but, as the Ferret system was used mainly in remote localities, a subset (n=728, 37.1%) of these children had a Ferret record as well as a PDC record. The mothers and babies where the child had a Ferret record were compared with the mothers and babies where the child did not have a Ferret record. These comparisons were made to assess if relying on information from the Ferret data system would introduce any systematic bias in the subsequent analysis.

Definitions of key characteristics

Key characteristics of the mothers, babies and young children are presented here to describe the information obtained; for example, body mass index of mothers, prematurity of babies. For mothers, conditions in pregnancy (anaemia, gestational diabetes and pregnancy-induced hypertension) are as reported in the Perinatal Data Collection (PDC). Other definitions are those used by the National Health and Medical Research Council, the Australian Institute of Health and Welfare and the Australian Bureau of Statistics. For details of the definitions used, see Supplementary Table 3. World Health Organization (WHO) guidelines for use of the WHO Child Growth Standards were followed.[31,32] Weight and height measurements that resulted in weight for age or height for age z-scores of less than -6 or greater than +5 (weight for age) or +6 (length/height for age) were considered implausible values.[31,33]

Results

The process of approvals, data extraction and preparation of the linked data took 23 months from ethics approval. Six interim releases were made as data became available, at the researchers' request. Supplementary Table 2 provides more detail. The information secured for each of the two cohorts of mothers and their children is summarised below.

The Cape York Child Growth Cohort 2006 to 2008

Perinatal data records for birth were provided for 380 children born in 2006, 2007 or 2008 and their mothers (n=339); 87.6% of the 434 children included in previous research. To ensure independence of events for subsequent statistical analysis, children who were not the first birth to a mother during those three years (n=40) and second-born twins (n=3) were excluded, leaving records for 337 unique mother–child pairs. The process of exclusions and results of linkage with other data collections are shown in Figure 1.

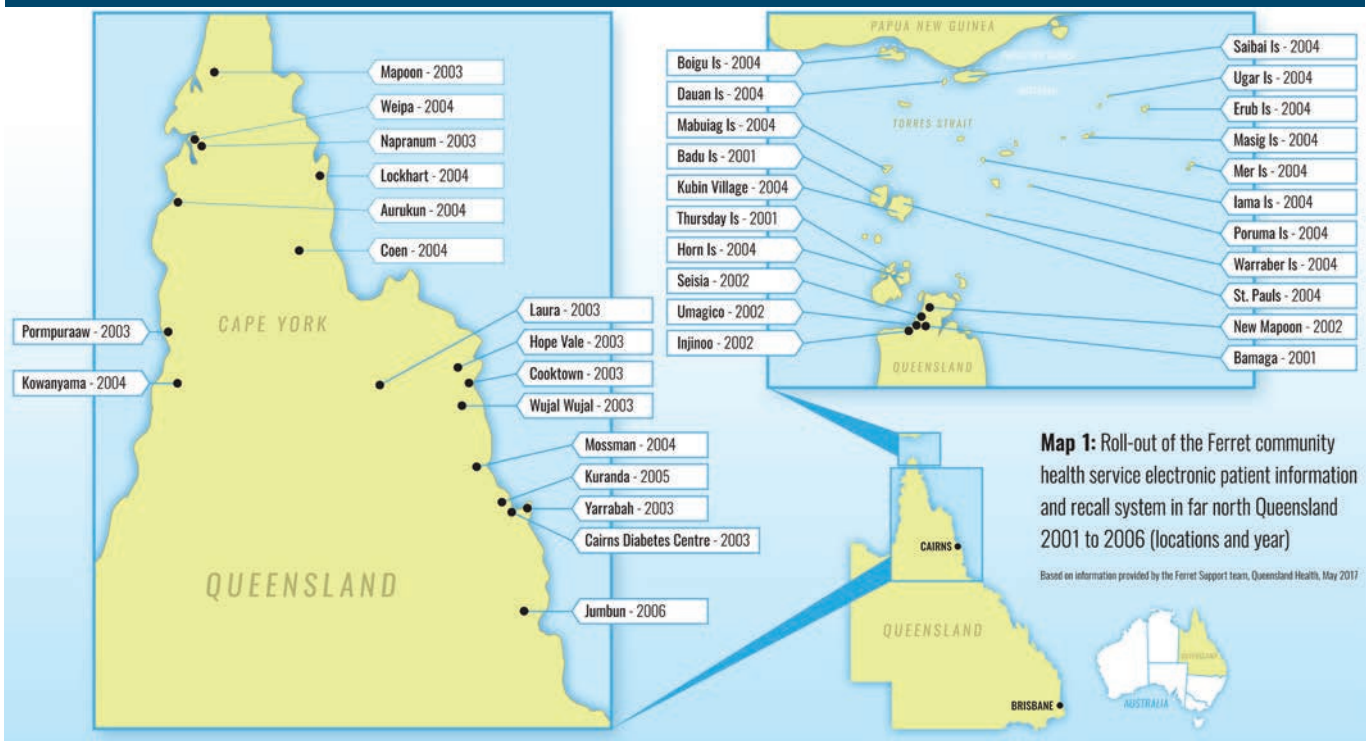
Key descriptive information for these 337 mothers and their babies at birth is shown in Table 2.

The 2009 and 2010 birth cohort

Perinatal Data Collection records for birth were provided for 2,167 babies born to 1,993 Aboriginal and/or Torres Strait Islander mothers in 2009 or 2010 in Far North Queensland. Of these, 20 babies were stillborn and 11 died as neonates, leaving 2,136 surviving babies.

Children who were the second baby (n=154) or third baby (n=1) born to the same mother in that two-year period and 16 babies who

Figure 1: The rollout of Ferret in Far North Queensland 2001 to 2006.



were the second-born of twins are excluded from this report, leaving information for 1,965 unique mother–child pairs. The process of exclusions and results of linkage with the other data collections are shown in Figure 2. Descriptive information for these mothers and their babies (n=1,965) and for the subset of mothers and babies (n=728) with longitudinal information from the Ferret system is shown in Table 2.

Data quality and completeness

The quality and completeness of the data provided varied between different data sources with different variables, as shown in Table 3. Information from the Perinatal Data Collection (PDC) was complete for some variables (mothers' dates of birth, the date of birth and sex of babies, birth weight, plurality and method of birth). More information was missing in respect of mothers' weights, heights and parity. The proportion of missing PDC information reduced over time. Pathology measurements of haemoglobin were available for most mothers (Cape York mothers, 87.8%; 2009 and 2010 birth cohort mothers 97.0%) and, to a lesser extent, measurements of glucose tolerance and iron status. For most mothers (between 73.5% and 85.9%) information on folate and vitamin B_{12} levels was not available.

Comparisons with census information

Data completeness was also assessed by comparison of child numbers and information on the ethnicity of mothers with census information for remote areas.

Cape York Child Growth cohort

For the Cape York communities, Census 2006 results show 427 resident children who were born in the three years preceding the August 2006 Census. This number is close to the 434 children included in the previous research project, although somewhat higher than the 380 children for whom a record of birth between 2006 and 2008 was located on the Perinatal Data Collection.

2009 and 2010 birth cohort

The locations where the Ferret system was used, as shown in Figure 1, were mainly in Cape York (n=12) and in the Torres Strait (n=21). When Census 2011 population figures are combined for Torres Strait and Cape York, the total population of Aboriginal and Torres Strait Islander children under five years of age is 1,830. On a pro-rata basis, this is equivalent to 732 children who were born in any two-year period from Census 2006 to Census 2011.[34] This figure is close to the number of children (n=728) identified by this research who were born in 2009 and 2010 and who had both Perinatal Data Collection and Ferret records.

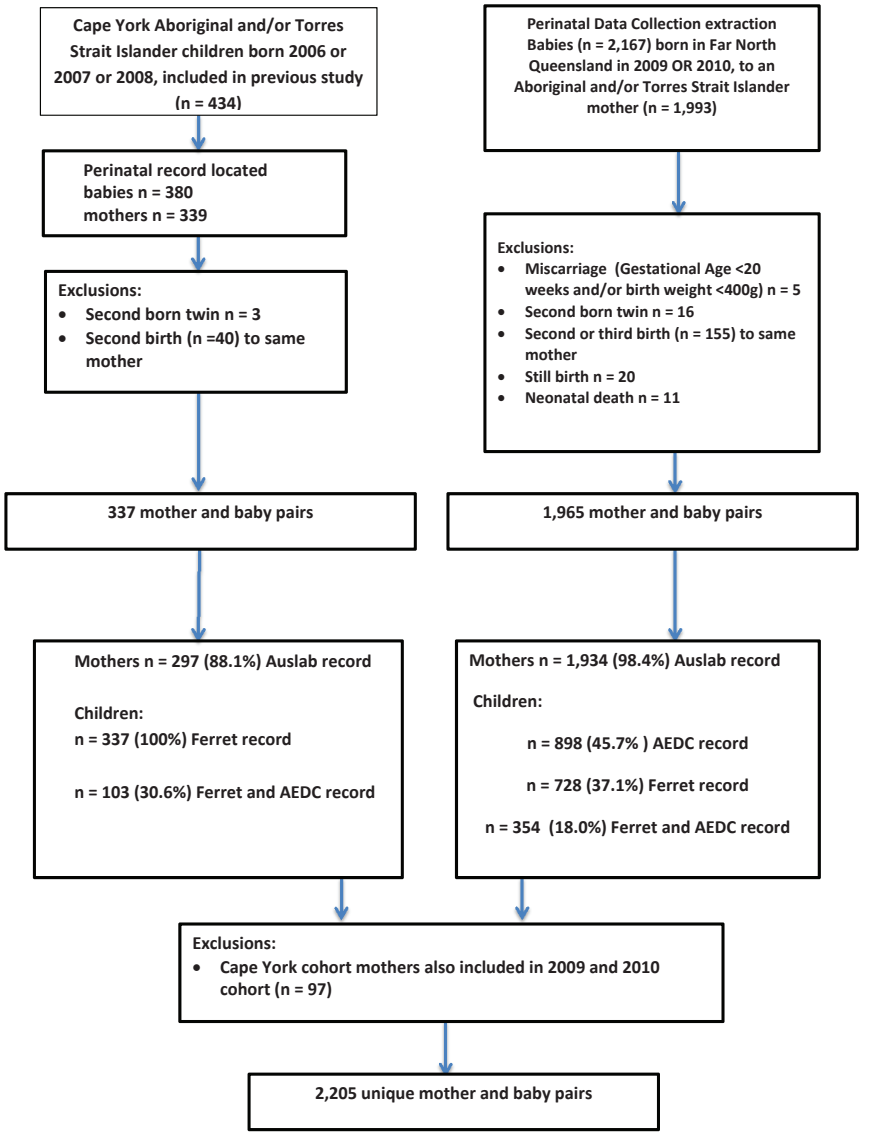
Information in respect of ethnicity of mothers is shown in Supplementary Figures 1a and 1b. The ethnicity of the mothers from Cape York and the Torres Strait who were included in both cohorts is consistent with information on ethnicity of residents of Cape York and the Torres Strait as reported in the 2011 Census.

Comparing mothers and babies with a child Ferret record and those without a child Ferret record

Differences for mothers were found in respect of residence in a remote location (PDC only: 7.8% remote residence vs. PDC and Ferret: 86.3% remote residence; $p<0.001$), in ethnicity and in gestational diabetes in pregnancy. Mothers whose child had a Ferret record were more likely to be Torres Strait Islander (51.1% vs. 24.8%) and less likely to be Aboriginal (37.4% vs. 61.9%; $p<0.001$). More mothers whose child had a Ferret record had gestational diabetes (12.1% vs. 9.2%, $p=0.043$). No other significant difference was seen in respect of the mothers or their babies at birth. The results of this comparison are shown in Supplementary Table 4.

Subsequent merging of information for the two cohorts of mothers and babies identified 97 mothers in the 2009–2010 birth cohort (n=1,965), who were already included in the earlier Cape York Child Growth cohort. Excluding these 97 duplicate mothers and their later babies reduced the numbers

Figure 2: Flow diagram – data provided and exclusions for both cohorts.



of mother–baby pairs in the 2009–2010 cohort to 1,868 pairs. In total, therefore, this work assembled intergenerational health information for 2,205 Aboriginal and Torres Strait Islander mother–baby pairs from Far North Queensland where the child was the first child born to that mother between 2006 and 2010.

Discussion

The work described here has resulted in a dataset with longitudinal intergenerational information for 2,205 Aboriginal and Torres Strait Islander mother–child pairs from prior to pregnancy, through pregnancy, from birth and through early childhood to the first year of school, recorded over a period of 15 years. The process of obtaining these data was lengthy (23 months) but was much less time than the 15-plus years required for a prospective study with an equivalent timespan.

The release of earlier versions, as each stage of linkage was completed, enabled the researchers to become familiar with the dataset. This process allowed gaps and errors to be identified and rectified. Preparatory analysis – of child growth parameters, for example – was undertaken prior to the release of the completed linkage file.

Comparisons with census information showed consistency in respect of child participant numbers and the ethnic mix of mothers from remote localities.[34] Differences in regional boundaries used by various government entities meant it was difficult to make similar comparisons for non-remote locations. However, the comparison between those mothers and babies where the child had a subsequent Ferret record and those where the child did not have a Ferret record was effectively a comparison of remote and non-remote participants. These comparisons found few differences, apart from remote residence, ethnicity and diabetes in pregnancy. These findings reflect the high Ferret coverage in the Torres Strait where the incidence of diabetes in pregnancy is particularly high.[35]

The researchers will analyse the data to investigate anaemia among these Aboriginal and Torres Strait Islander mothers and their children. Risk factors for early childhood anaemia that relate to the health of mothers will be explored (age, parity, anaemia, iron status and glucose tolerance) and factors relating to the child (birth weight, gestational age, early infant feeding, rate of growth). Information on early childhood development indicators at school entry will be used to assess the consequences of early childhood anaemia.

There were some issues of data quality and completeness, although reductions in missing values over time indicate ongoing quality improvement. For the analysis, we will use the STATA statistical package (Stata version 13, StataCorp, Lakeway Drive, College Station, Texas) to enable us to conduct multivariable analysis, with and without data imputation, to gauge the impact of missing information on the outcome measures.[36]

An inquiry by the Productivity Commission into the use of existing data collections recommended greater transparency and changes in the legal framework to increase accessibility, which may shorten the time required for approval processes in future.[37] However, access to existing data collections entails ethical and legal considerations including issues of privacy and confidentiality that require time for proper consideration. This is particularly true for research relating to Aboriginal and Torres Strait Islander peoples.[38]

The recently endorsed Australian National Digital Health Strategy should provide a framework for integrated health service data systems, replacing the current data silos.[2] In Far North Queensland, there has been an increase in community-controlled health service providers in recent years. An integrated health service data system will have benefits for service provision with

Table 2: Key Characteristics of each cohort - Mothers and their babies at birth, including the subset of the 2009 and 2010 birth cohort where the child had a Ferret longitudinal record of growth and haemoglobin measurements.

	Cape York Child Growth	All 2009 & 2010 Births	2009 & 2010 Births with Ferret record
	Mothers (n=337)	**Mothers (n=1,965)**	**Mothers (n=728)**
Ethnicity			
Aboriginal	286 (84.9%)	1,038 (52.8%)	272 (37.4%)
Torres Strait Islander	18 (5.3%)	679 (34.6%)	372 (51.1%)
Aboriginal and Torres Strait Islander	18 (5.3%)	248 (12.6%)	84 (11.5%)
Non-Indigenous	15 (4.5%)	–	–
Location usual residence			
Torres & NPA	3 (0.9%)	443 (22.5%)	375 (51.5%)
Cape York	298 (88.4%)	304 (15.5%)	270 (37.1%)
Other FNQ	26 (7.7%)	1,199 (61.0%)	78 (10.7%)
not FNQ	10 (3.0%)	19 (1.0%)	5 (0.7%)
Age years mean (SD) range	24.9 (6.4) 15–41	25.3 (6.4) 13–48	25.0 (6.2) 13–48
Parity median (range)	2 (0–8)	2 (0–16)	2 (0–10)
Body Mass Index (BMI) (kg/m2)	n=122	n=1,834	n=679
mean (SD), range	23.7 (5.8), 14.9–37.7	27.1 (6.6), 14.3–55.9	27.4 (6.8), 14.3–55.9
Body Mass Index categories			
Under-weight	28 (23.0%)	114 (6.2%)	51 (7.5%)
Healthy weight	46 (37.7%)	684 (37.3%)	225 (33.1%)
Over-weight	31 (25.4%)	456 (24.9%)	167 (24.6%)
Obese	17 (13.9%)	580 (31.6%)	236 (34.8%)
Perinatal Data Collection (PDC) - pregnancy information			
Anaemia	14 (4.2%)	75 (3.8%)	28 (3.9%)
Gestational Diabetes	11 (3.6%)	202 (10.3%)	88 (12.1%)
Pregnancy Induced Hypertension	27 (7.4%)	96 (4.9%)	35 (4.8%)
Smoking	215 (64.6%) (n=333)	1,113 (56.8%) (n=1,960)	426 (58.9%) (n=726)
	Babies (n=337)	**Babies (n=1,965)**	**Babies (n=728)**
Boys/Girls	51.3%/48.7%	54.0%/46.0%	52.9%/47.1%
Gestational Age weeks median, range	39, 27–42	39, 22–43	39, 26–42
Premature n (%) (95% CI)	40 (11.9%) (8.4%, 15.3%)	209 (10.7%) (9.3%, 12.0%)	76 (10.4%) (8.2%, 12.7%)
Birth Weight[a] grams mean (SD) range	3,089 (602.3) 800–5,320	3,247.1 (629) 495*–5,430	3,273 (600) 960–5,050
Low birth weight (<2,500g)	45 (13.4%)	196 (10.0%)	65 (8.9%)
High birth weight (>= 4,000g)	15 (4.5%)	185 (9.4%)	62 (8.5%)

Notes:
a: baby with birth weight 495g was recorded as a live birth - there is nil record of neonatal death for this baby

this welcome increased diversity of service providers – and benefits for future data linkage for research.

Implications for public health

The work described in this report has secured a dataset of linked information from four health data collections and one education data collection, which will be a valuable resource in investigating the issue of anaemia among Aboriginal and Torres Strait Islander mothers and their children in Far North Queensland. This report illustrates how the linkage of existing data resources can provide intergenerational information for health research. However, the true value of the resultant data collection will be demonstrated by the subsequent planned research and reporting. To use a nutrition-related analogy, the proof of the pudding will be in the eating.

Acknowledgements

We would like to acknowledge and thank the Aboriginal and Torres Strait Islander leaders of the key community-controlled health service organisations in Far North Queensland who considered and endorsed the proposed research, providing the support that made this research possible.

In addition, we acknowledge and thank the Data Custodians and their research and data management staff.

We especially want to acknowledge the contributions of the following people:

- Staff of the Queensland Health Statistical Services Branch, with particular thanks to Rachel Garry for support for Public Health Act applications and variations, and to Dale Steinhardt for data extraction and linkage.
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- Staff of the Queensland Pathology Clinical Information Systems Support Unit, with particular thanks to Wanda Sprenger for data extraction.

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Table 3: Data quality – missing, implausible, and available data – examples from four[a] data collections.

	Cape York Child Growth Born 2006 – 2008	2009 & 2010 Births
	n=337 mother and baby pairs n=337 with Ferret longitudinal record	n=1,965 mother and baby pairs n=728 with Ferret longitudinal record
	n (%)	n (%)
Perinatal Data Collection – missing information		
Mothers		
Ethnicity	nil	nil
Location usual residence	nil	nil
Date of birth	nil	nil
Smoking in pregnancy	4(1.2%)	5 (0.3%)
Parity	109 (32.3%)	526 (26.8%)
Weight	190 (56.4%)	79 (4.0%)
Height	196 (58.2%)	117 (6.0%)
Weight and/or Height	204 (60.5%)	136 (6.9%)
Babies – missing information		
Birth weight	nil	1 (0.05%)
Gestational age at birth	nil	5 (0.3%)
Sex	nil	nil
Ferret – child records		
Inconsistent ethnicity records	nil	9 (1.2%)
Date of measurement prior to date of birth	nil	15 (0.2%, n=8,539)
Implausible weight measurements	170 (2%, n=8,328 measurements)	45 (0.6%, n=7,150 measurements)
Implausible lengths/heights	28 (2.3%, n=1,202 measurements)	45 (1.7%, n=2,622 measurements)
Auslab data missing for mothers		
Haemoglobin record in cohort pregnancy	41 (12.2%)	59 (3.0%)
Iron status record for mother in cohort pregnancy	125 (37.1%)	752 (38.3%)
Glucose tolerance before or during pregnancy	31 (10.3%)	583 (29.7%)
Folate measurement before or during pregnancy	277 (73.5%)	1,552 (79.0%)
Vitamin B12 measurement before or during pregnancy	324 (85.9%)	1,603 (81.6%)
Australian Early Development Census record available (child) – 2012	103 (30.6%)	n/a
Australian Early Development Census record available (child) – 2015	n/a	898 (45.7%)

Notes:

a: Only some children would have been admitted to hospital, so it is not possible to ascertain if Queensland Hospital admission records are missing

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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary Table 1: Data Collections used to source information for planned research to investigate maternal and early childhood anaemia.

Supplementary Table 2: Time frame for Queensland Public Health Act approvals, data linkage and release.

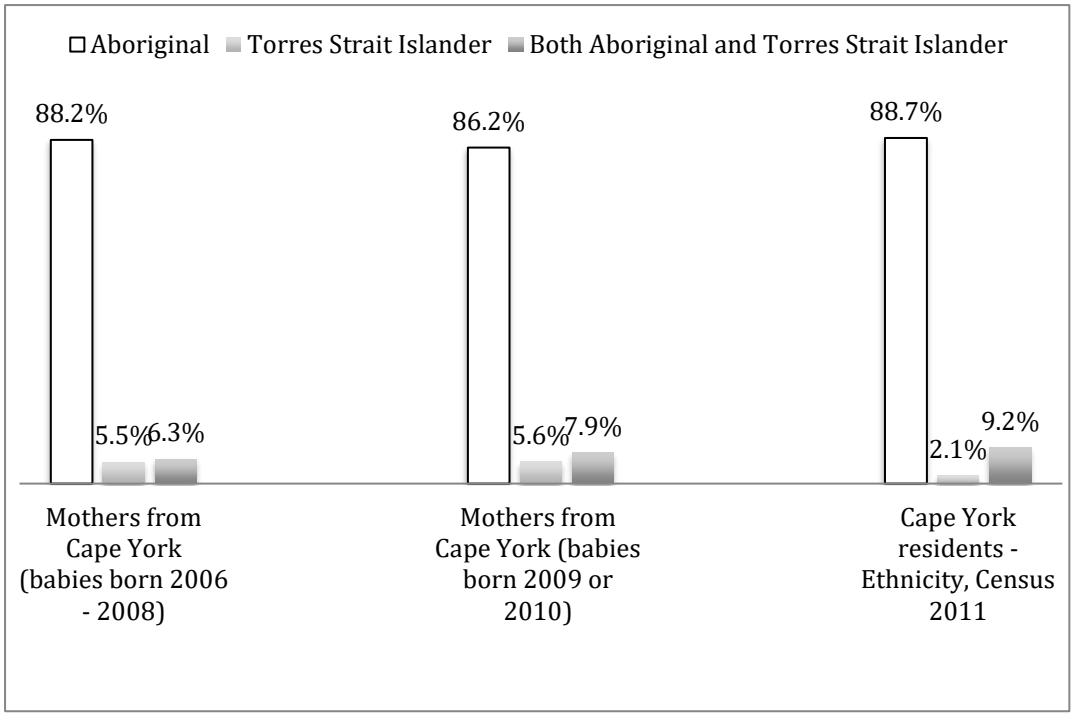
Supplementary Table 3: Definitions of variables .

Supplementary Table 4: 2009 and 2010 birth cohort: comparing characteristics of mothers and babies where the child had a Perinatal Data Collection (PDC) record only compared to mothers and babies where child had both a PDC and a Ferret record.

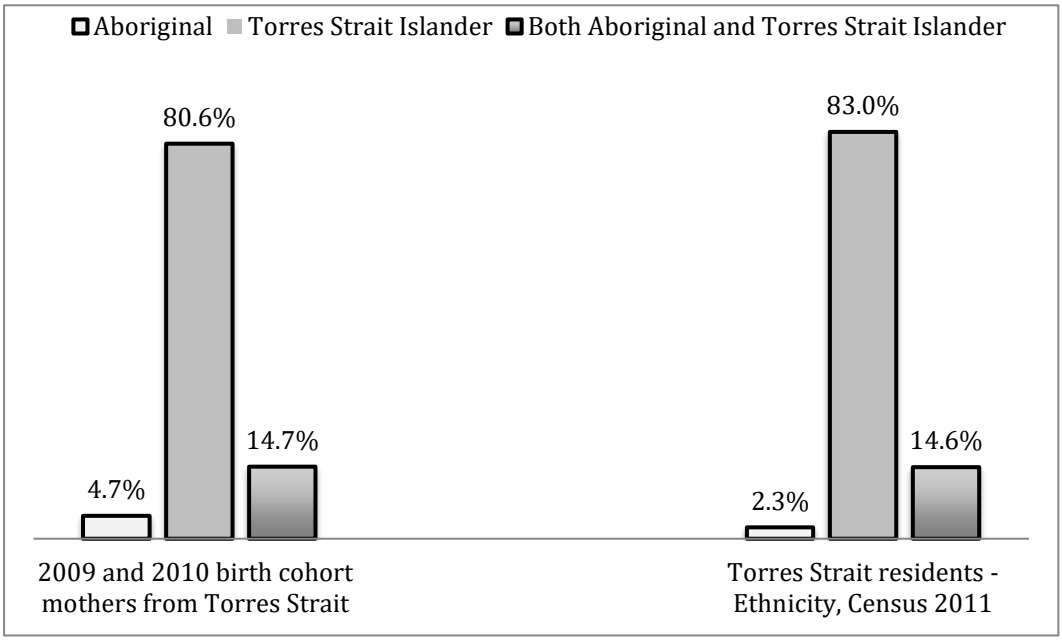
Supplementary Figure 1a: Comparison with Census 2011 – ethnicity of mothers from Cape York.

Supplementary Figure 1b: Comparison with Census 2011 – ethnicity of mothers from Torres Strait.

2.2 Supplementary Materials



Supplementary Figure 2.1 Comparison with Census 2011 - ethnicity of mothers from Cape York.



Supplementary Figure 2.2 Comparison with Census 2011 - ethnicity of mothers from the Torres Strait.

Supplementary Table 2.1
Data Collections used to source information for planned research to investigate maternal and early childhood anaemia.

Year commenced	Data Collection
1986	Queensland Perinatal Data Collection (PDC) Information on Queensland mothers and their babies is recorded at the time of birth on the Perinatal Data Collection, which commenced in Queensland in 1986. Information is collected on all live births in Queensland and on all stillbirths of at least 20 weeks gestation and/or at least 400g in weight.[1]
1999	Queensland Hospitals Admitted Patient Data Collection (QHAPDC) Information is recorded on the Queensland Hospitals Admitted Patient Data Collection for all patients admitted to public and private hospitals in Queensland since 1999. Information recorded includes the reasons for admission using the World Health Organization International Classification of Disease and information on type of separation (discharge, transfer, death).[2]
2001	Ferret A centralised electronic patient information and recall system rolled out in health services in far north Queensland from 2001 to 2006.[3 4] Ferret was used mainly by community health services in thirty three remote Aboriginal and Torres Strait Islander communities (Torres Strait (n = 21) and Cape York (n = 12)) plus five locations in the vicinity of Cairns. The Ferret system rollout was completed in 2006. Data recorded on Ferret includes information from routine adult health checks, antenatal and child health checks.
1999	Auslab: Pathology Queensland provides pathology services to all Queensland Health facilities. Pathology test results are recorded on centralised electronic systems. The Auslab system which commenced in 1999 was in use for this purpose during the timeframe of this research. [5]

Year commenced	Data Collection
2009	The Australian Early Development Census (AEDC) Data Collection Every three years, the Australian Department of Education the conducts the Australian Early Development Census. Every child commencing full time school in that year in Australia is assessed by his/her teacher for early childhood development in respect of: • Physical health and well-being • Social competence • Emotional maturity • Language and cognitive skills • Communication and general knowledge Each child is allocated a composite score and assigned to one of three categories: on track, at risk, or vulnerable Approximately one third of the children included in this study were potential participants for the Australian Early Development Censuses conducted on children enrolled in their first full time year of school, in 2012 or 2015. [6]

Supplementary Table 2.1 References

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Supplementary Table 2.2
Time frame for Queensland Public Health Act approvals, data linkage and release.

Date	Milestone
June 2015	Ethics approval granted by Cairns and Hinterland Human Research Ethics Committee HREC/15/QCH/50 - 980 SEP
	Endorsed by James Cook University Human Ethics Research Committee August 2015 *Data custodian approvals: Ferret/Auslab November 2015* *Perinatal Data Collection (PDC)/Queensland Hospitals Admitted Patients Data Collection (QHAPDC) February 2016*
February 2016	Queensland Health Public Health Act Approval (PHAA) granted
June 2016	Version 1 of linkage file released (PDC, QHAPDC, Ferret)
	Linkage key between mothers and babies missing *Requirement for an additional approval process for the release of Queensland Pathology data flagged by linkage team*
July 2016	AEDC data custodian approval for release of microdata for AEDC 2012 and AEDC 2015
August 2016	Version 2 of linkage file released (PDC, QHAPDC, Ferret)
	Linkage key between mothers and babies included *QHAPDC information - insufficient date information* *Antenatal information for mothers was for years subsequent to birth of cohort children*
September 2016	Amendment to PHAA to link AEDC data approved
November 2016	Approval for release of Queensland Pathology (Auslab) information

Date	Milestone
November 2016	Version 3 of linkage file released (PDC, QHAPDC, Ferret) *QHAPDC dates issue resolved* *Ferret team confirmed that antenatal data not collected 'per se' prior to 2010* *Pregnancy complications information missing from the PDC data due to researcher error in the PHAA application*
December 2016	Version 4 of linkage file released (PDC, QHAPDC, Ferret plus AEDC linkage keys) *Analysis of growth parameters of children identified missing lengths for children < 2 years old prior to 2009* AEDC data set released
February 2017	Version 5 of linkage file released (PDC, QHAPDC, Ferret, Auslab plus AEDC linkage keys) *Auslab haemoglobin information for mothers missing for several years - due to transcription error* *Due to linkage of Auslab data, mother and baby identification numbers differed from previous releases* *Ferret information for children of one cohort missing while other cohort children included twice*
March 2017	Version 6 of linkage file released (PDC, QHAPDC, Ferret, Auslab plus AEDC linkage keys) *All Auslab haemoglobin information for mothers included* *Children from both cohorts included* *PHAA Amendment approved for release of PDC pregnancy complications information*
April 2017	Version 7 of linkage file released (PDC, QHAPDC, Ferret, Auslab plus AEDC linkage keys) *PDC Pregnancy Complications Information included* *Information missing for mothers of one cohort while provided twice for the other mothers*
May 2017	Missing information for mothers provided for linkage file version 7

Supplementary Table 2.3
Definitions of variables.

Mothers	**Definition**
Maternal age	Age in completed years of the mother on day her baby is born
Body Mass Index	Weight in kilograms divided by (height in metres). [2]
Body Mass Index categories –18 years and older	BMI categories (underweight, healthy weight, overweight and obese) are defined as recommended by the National Health and Medical Research Council for mothers aged 18 years and over. [1]
Body Mass Index categories – under 18 years of age	For mothers aged less than 18 years at the time of the birth of the cohort baby BMI was categorised using cut-offs for females by 6 month age groups, as defined by Cole et al.[2, 3]
Babies	**Definition**
Miscarriage	Baby born with gestational age less than 20 weeks and/or birth weight less than 400g [4]
Prematurity	Gestational age less than 37 weeks. [5]
Low birth weight	Birth weight less than 2,500g. [6]
Macrosomia	Birth weight 4,000g or more. [4]
High Macrosomia	Birth weight of 4,500g or more. [4]
Stillbirth	Fetal death after 20 weeks gestation and before or during birth. [4]
Neonatal deaths	Death of a live born baby before the age of 28 days. [4]

Supplementary Table 2.3 References

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Supplementary Table 2.4

2009 and 2010 birth cohort: comparing characteristics of mothers and babies where the child had a Perinatal Data Collection (PDC) record only compared to mothers and babies where child had both a PDC and a Ferret record.

Mothers	**All mothers (n = 1,965)**	**Child PDC record only (n = 1,237)**	**Child PDC and Ferret record (n = 728)**	**p value ***
Ethnicity				
Aboriginal	1,038 (52.8%)	766 (61.9%)	272 (37.4%)	**P <0.001 (chi)**
Torres Strait Islander	679 (34.6%)	307(24.8%0	372 (51.1%)	
Aboriginal and Torres Strait Islander	248 (12.6%)	164 (13.3%)	84 (11.5%)	
Resident in remote community	725 (36.9%)	97 (7.8%)	628 (86.3%)	**P < 0.001 (chi)**
Age years mean (SD) range	25.3 (6.4) 13-48	25.5 (6.4) 13-45	25.0 (6.2) 13-48	P = 0.1189 (t)
Record of Parity	1,440 (73.3%)	923 (74.6%)	517 (71.0%)	P = 0.082 (chi)
Parity median (range)	2 (0 - 16)	2 (0 - 16)	2 (0 - 10)	P = 0.482 (w)
Body Mass Index (kg/m2)	n = 1,834	n = 1,155	n = 679	
mean (SD), range	27.1 (6.6) 14.3-55.9	27.0 (6.5) 14.5 – 54.8	27.4 (6.8) 14.3 – 55.9	P = 0.0594 (t)
Body Mass Index categories				
Under-weight	114 (6.2%)	63 (5.5%)	51 (7.5%)	P = 0.074 (np)
Healthy weight	684 (37.3%)	459 (39.7%)	225 (33.1%)	

Mothers	**All mothers (n = 1,965)**	**Child PDC record only (n = 1,237)**	**Child PDC and Ferret record (n = 728)**	**p value ***
Over-weight	456 (24.9%)	289 (25.0%)	167 (24.6%)	
Obese	580 (31.6%)	344 (29.8%)	236 (34.8%)	
Perinatal Data Collection (PDC) - pregnancy information				
Anaemia	75 (3.8%)	47 (3.8%)	28 (3.9%)	P = 0.958 (chi)
Gestational Diabetes	202 (10.3%)	114 (9.2%)	88 (12.1%)	**P = 0.043 (chi)**
Pregnancy Induced Hypertension	96 (4.9%)	61 (4.9%)	35 (4.8%)	P = 0.902 (chi)
Smoking	(n=1,113)	(n=687)	(n=426)	P = 0.187 (chi)
	(56.8%)	(55.7%)	(58.9%)	
	(n = 1,960)	n = 1,234	(n = 726)	
Babies				
Gestational Age weeks median, range	39, 22 - 43	39, 22 - 43	39, 26 - 42	P = 0.496 (w)
n = 1,963				
Premature n (%)	209 (10.7%)	133 (10.8%)	76 (10.4%)	P = 0.819 (chi)
Birth Weight grams mean (SD)	3,247.1 (629)	3,231.7 (645)	3,273 (600)	P = 0.496 (w)

Mothers	All mothers (n = 1,965)	Child PDC record only (n = 1,237)	Child PDC and Ferret record (n = 728)	p value *
Birth Weight categories				
Low (<2,500g)	196 (10.0%)	131 (10.6%)	65 (8.9%)	P = 0.906 (np)
Normal (2,500 - < 4,000g)	1,584 (80.6%)	983 (79.5%)	601 (82.6%)	
High (>= 4,000g)	185 (9.4%)	123 (9.9%)	62 (8.5%)	

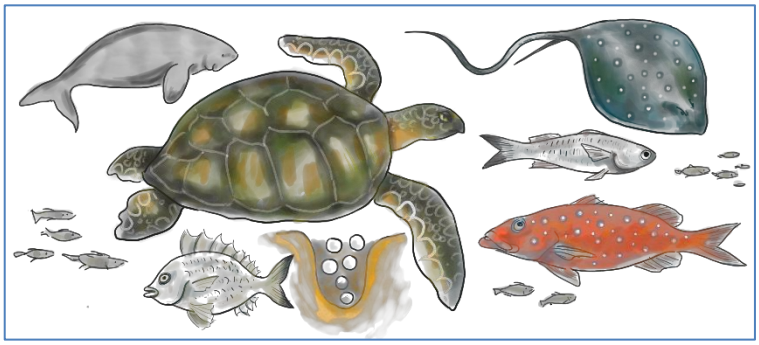
*brackets indicate statistical test used for comparisons
(chi) Chi-square test
(t) t-test
(w) two sample Wilcoxon (Mann-Whitney) rank-sum test
(np) non-parametric test for trend

Foreword Chapter 3 (Results 1)

In the previous chapters I have described the rationale for this research and the methods used. In Chapter 3, I present the results of this research in respect of the mothers. Descriptive information for the mothers includes demographic information, indicators of their health and nutrition status, the prevalence of anaemia in pregnancy among the mothers and the outcomes of their pregnancies. I investigate the association of these factors with anaemia in pregnancy among these mothers and the association of anaemia in pregnancy with their pregnancy outcomes.

The information presented in this chapter was published in *Nutrition and Dietetics* in November 2018;

Leonard D, Buttner P, Thompson F, Makrides M, McDermott R. Anaemia in pregnancy among Aboriginal and Torres Strait Islander women of Far North Queensland: A retrospective cohort study. Nutr Diet. 2018;75(5):457-67. https://doi.org/10.1111/1747-0080.12481



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Chapter 3 Anaemia in Pregnancy Among Aboriginal and Torres Strait Islander Women of Far North Queensland: a Retrospective Cohort Study

Table 3.1
List of Tables in article Anaemia in Pregnancy Among Aboriginal and Torres Strait Islander Women of Far North Queensland: a Retrospective Cohort Study.

Table 3.2
List of Figures in article Anaemia in Pregnancy Among Aboriginal and Torres Strait Islander Women of Far North Queensland: a Retrospective Cohort Study.

3.1 Article: Anaemia in Pregnancy Among Aboriginal and Torres Strait Islander Women of Far North Queensland: a Retrospective Cohort Study

Nutrition & Dietetics 2018; **75**: 457–467 DOI: 10.1111/1747-0080.12481

ORIGINAL RESEARCH

Anaemia in pregnancy among Aboriginal and Torres Strait Islander women of Far North Queensland: A retrospective cohort study

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Abstract

Aim: Anaemia during pregnancy is common worldwide. In Australia between 7.1% and 11% of mothers have been reported to have anaemia in pregnancy. Higher rates are reported for Aboriginal and Torres Strait Islander women (Townsville: 34.2%, remote Northern Territory: 50%). The present study describes anaemia in pregnancy among Aboriginal and Torres Strait Islander women of Far North Queensland.

Methods: Health service information was analysed for 2076 Aboriginal and Torres Strait Islander women who gave birth between 2006 and 2010. The prevalence of anaemia in pregnancy, characteristics of the mothers and pregnancy outcomes were described. Logistic regression for bivariate analyses and multivariable linear modelling with and without imputed data were used to compare those mothers who had anaemia in pregnancy with those who did not.

Results: More than half of Aboriginal and Torres Strait Islander women (54.5% (95% CI: 52.4%, 56.7%)) had anaemia in pregnancy. For mothers who gave birth in 2009 and 2010 (n = 1796) with more complete data, those who were iron deficient during pregnancy were more likely to be anaemic (RR: 1.40, $P = <0.001$). Mothers (29.0%) from localities of relative socioeconomic advantage had lower risk of anaemia in pregnancy (RR: 0.86, $P = 0.003$), as did mothers (31.9%) who were obese (RR: 0.87, $P = 0.013$).

Conclusions: The prevalence of anaemia in pregnancy among Aboriginal and Torres Strait Islander women of Far North Queensland is high. Prevention and treatment of anaemia will improve the health of these mothers, and possibly the health and early development of their children.

Key words: Aboriginal, anaemia, mother, pregnancy, Torres Strait Islander.

Introduction

The 'First Thousand Days' from conception to around age 2 years is a time of rapid growth and neurological development.[1,2] Anaemia in pregnancy—defined as blood haemoglobin levels below 110 g/L—is a concern because of poorer health and pregnancy outcomes of mothers, and also the potential detrimental effects on the health and development of their children.[1,3]

Infections, inflammation and genetic conditions (e.g. thalassaemia) can cause anaemia, as well as iron deficiency and other nutritional deficiencies.[3] Although an essential nutrient, iron can have negative metabolic effects.[4] To prevent damage, iron absorption is tightly regulated but increases when iron requirements are high, as in pregnancy.[4] The pregnant mother requires iron not only for her immediate demands—increased blood, tissue growth—but to provide iron stores to her baby.[5] The main source of iron for a baby in the first months of life is not breast milk or infant formula but these iron stores acquired before birth.[5] The high maternal iron requirements mean that anaemia in pregnancy is usually due to iron deficiency and is a strong predictor of early onset anaemia in the child.[3,6] High rates of early childhood anaemia are a continuing concern in remote Aboriginal and Torres Strait Islander communities of northern Australia.[7,8]

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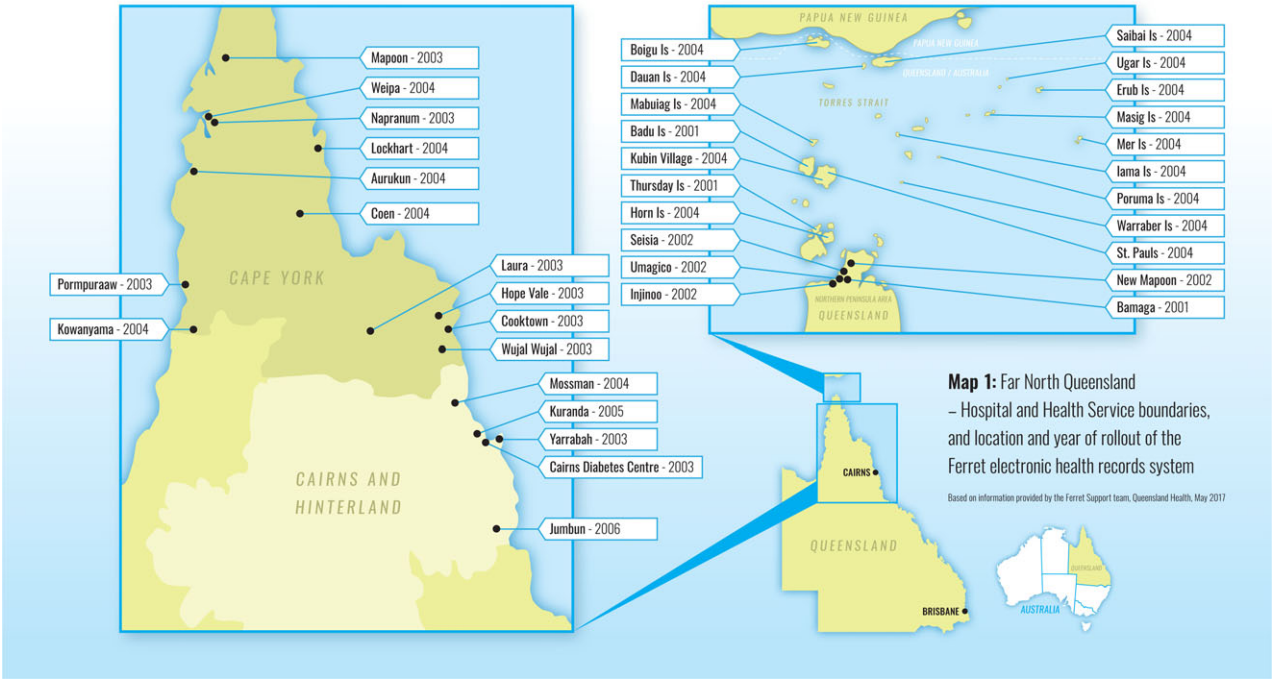

Figure 1 Far North Queensland: Hospital and Health Service boundaries, and location and year of rollout of the Ferret electronic health records system. Based on the information provided by the Ferret Support team, Queensland Health, May 2017. Reproduced with permission of the Australian New Zealand Journal of Public Health.[14]

Australian studies reporting anaemia in pregnancy include studies from South Australia (unsupplemented control group: 11% anaemic, births 1997–1999, including 3.3% Aboriginal mothers), Western Australia (6.2% anaemic >18 years, births 2005–2006, 7.3% Aboriginal and Torres Strait Islander mothers) and for all births in South Australia 1999–2005 (7.1% anaemic, 2.5% Aboriginal and Torres Strait Islander mothers).[9–11] Higher rates of anaemia in pregnancy have been reported for Aboriginal and Torres Strait Islander women accessing antenatal care in Townsville (34.2% anaemic, births 2001–2003) and in two remote Northern Territory communities (50.0% anaemic, births 2004–2006).[12,13]

Anecdotal reports by health service providers in Far North Queensland (Figure 1) indicate that anaemia among Aboriginal and Torres Strait Islander mothers and their children is also prevalent but published information is lacking. Consequently, research has been undertaken to investigate anaemia among Aboriginal and Torres Strait Islander mothers and their children in Far North Queensland from an intergenerational perspective. Here we describe anaemia in pregnancy, and investigate associations between anaemia and various maternal characteristics, health indicators, and pregnancy outcomes of these mothers for a pregnancy and birth between 2006 and 2010.

Methods

This is a retrospective cohort study using linked information extracted from three existing health service data collections for mothers resident in Far North Queensland, in respect of pregnancies and births of their babies born between 2006 and 2010.

Data sources: Electronic data systems used by health service providers store confidential client information with strict provisions for data security and confidentiality. However de-identified information may be released for research purposes, subject to stringent processes to ensure data security and confidentiality. The process of securing the necessary approvals and release of a linked, de-identified dataset has been described elsewhere.[14] Briefly, data collections accessed were the Queensland Perinatal Data Collection (PDC); the Queensland Health Pathology Services Data Collection (Auslab); and the community health services electronic record system, Ferret, used mainly in remote locations of Far North Queensland (Supporting information Table S1). Information extracted from Auslab had been recorded from 2000 up to 2010, from Ferret from date of rollout (see Figure 1), up to 2010 and from PDC from 2006 to 2010. Individual records were linked and de-identified by the Queensland Health Statistical Services Branch for release to the research group in May 2017.

Participants: Study data were extracted from these data collections for two cohorts—the Cape York cohort and the 2009–2010 cohort.

The Cape York cohort includes mothers of Aboriginal and Torres Strait Islander children born between 2006 and 2008, where the child had previously been included in an unpublished health service review of childhood growth in remote Cape York communities.

The 2009–2010 cohort includes all Aboriginal and/or Torres Strait Islander mothers with a PDC record for a birth in 2009 or 2010 in Far North Queensland.

As children were recruited to the Cape York child growth research after the neonatal period, information on perinatal mortality is not available for the Cape York cohort. Perinatal mortality information is available for babies of the 2009–2010 cohort.

Ethics approval was granted by Queensland Health Far North Queensland Human Research Ethics Committee (HREC/15/QCH/50-980) in June 2015. Subsequent to applications to the respective Data Custodians for data release, approval under the Queensland Public Health Act 2005 was granted by the Director General of Queensland Health in February 2016.

Variables and definitions: Anaemia in pregnancy was defined as haemoglobin less than 110 g/L as used by Queensland Health.[15,16] Measurements of haemoglobin used here are results of pathology laboratory measurements. Iron deficiency was defined as Ferritin levels below 15 ug/L.[15]

Information recorded on the PDC includes mothers' ethnicity, parity, pre-pregnancy weight, height, smoking in pregnancy; birth status of babies—live/still born, gestational age at birth. Other information was derived from PDC records (maternal age, teenage mothers, body mass index categories, prematurity and birthweight category) as defined by the Australian Institute of Health and Welfare and the National Health and Medical Research Council—see Table S2.[17–19] Pre-existing diabetes was defined as a fasting oral glucose tolerance test result ≥7.0 mmol/L and/or a glycated haemoglobin reading ≥6.5%. Gestational diabetes was defined as an oral glucose tolerance test result ≥5.1 (fasting) and/or 10.0 (1 hour) and/or 8.5 mmol/L (2 hours) among women without pre-existing diabetes.[16,20,21] For definitions of hypertension, iron deficiency, low red cell folate (RCF) and vitamin B12 levels, see Table S2. Information on food insecurity, diet or nutrient supplements are not recorded in these electronic data collections.

The Socio-Economic Index for Areas (SEIFA 2011) ranks Australian Bureau of Statistics Statistical Local Areas (SLAs) by deciles of relative socioeconomic advantage and disadvantage.[22] A ranking of '1' indicates a locality of greatest relative disadvantage while a ranking of '10' indicates a locality of greatest relative advantage.[22] The appropriate SEIFA decile ranking was allocated to each mother based on her usual place of residence. For the purpose of this analysis, SEIFA deciles (1–10) were reduced to two categories: SEIFA deciles 1 and 2 (the 20% most disadvantaged SLAs in Australia) or SEIFA decile 3 or higher. These categories were selected as most of the mothers in this study (71.1%) lived in SEIFA categories 1 and 2.

Statistical analysis: Categorical variables were described using absolute and relative frequencies. The distribution of numerical variables were assessed; symmetrically distributed numerical characteristics were described using mean values, SDs and ranges; numerical values with a skewed distribution (parity, Ferritin levels, baby's gestational age at birth) were described using median, interquartile ranges (IQRs) and ranges. The prevalence of anaemia was presented with 95% confidence intervals (95% CIs).

Bivariate analysis: Characteristics of the mothers and their pregnancy outcomes were compared between those mothers who had been anaemic in pregnancy and those who had not, using logistic regression.

Multivariable analysis: The following characteristics were considered during multivariable analyses (Cohort 1 '2009–2010 cohort' n = 1796; Cohort 2 'Cape York cohort' n = 280). Variables with complete dataset were ethnicity of mother, age of mother, SEIFA category for residence of mother, five or more antenatal care visits, pregnancy induced hypertension, birthweight of baby (Cohort 2: complete dataset). Variables with missing values were: BMI category of mother, parity, smoking during pregnancy, mother with pre-existing diabetes, gestational diabetes, low RCF value before or during pregnancy, low vitamin B12 value before or during pregnancy, iron deficiency during pregnancy, birthweight of baby (missing values Cohort 1). The number of missing values for variables used in multivariable analyses is shown in Tables 1–2 and Tables S1-S4.

'*Missing-ness*': Examination of patterns of missing data showed data missing for some key variables; year of birth of baby (that is, the cohort) was significantly associated with missing body mass index ($P < 0.001$), missing parity ($P = 0.042$), and missing iron status ($P < 0.001$), resulting in more missing data for the Cape York cohort mothers. Consequently it was decided to conduct analysis stratified by cohort. Tables S3 and S4 provide more information on missing values and patterns of 'missing-ness'.

Multivariable general linear models for the binomial family using the log link to estimate relative risks (RRs) were used to identify independent risk factors for anaemia during pregnancy for the complete case analysis. Backward and forward stepwise modelling procedures were initially conducted to establish basic multivariable models for both cohorts. Characteristics that were not part of the basic models were assessed for potential confounding effects. A confounder was assumed to be a variable that changed estimates of characteristics in the basic model by 10% or more.[23] Once a model was established, all possible two-way interactions involving variables in the model were assessed for statistical significance.

Multiple imputation: Multivariate multiple imputation was conducted using Stata's MI commands for sequential imputation using chained equations. Missing values were imputed for BMI of mother; parity; smoking during pregnancy; mother with pre-existing or gestational diabetes; iron deficiency during pregnancy; and birthweight of baby. Low RCF and vitamin B12 values before or during pregnancy were not imputed because these characteristics were missing in close to 80% of cases in both cohorts and they did not show statistically significant associations during bivariate or multivariable complete case analyses. Before imputation, patterns of missing values were investigated and assumed to be 'missing at random' in each cohort.[24] Linear regression was used to impute missing values of continuous characteristics; logistic regression was used to impute missing values of dichotomous characteristics. Imputation models were based on the

Table 1 Prevalence of anaemia during the cohort pregnancy by characteristics of mothers, 2009–2010 cohort

Characteristics of mothers (data available and data missing[1])	*Mothers (n)*	*Mothers with anaemia in cohort pregnancy (n)*	*Prevalence of anaemia in pregnancy, % (95% CI)*	*P-values (logistic regression)*
All	1796	976	54.3% (52.0%, 56.6%)	—
Ethnicity[1] (complete dataset)				
Aboriginal	910	493	54.2% (50.9%, 57.4%)	Base
Torres Strait Islander	653	363	55.6% (51.8%, 59.4%)	0.58
Both Aboriginal and Torres Strait Islander	233	120	51.5% (45.0%, 58.0%)	0.465
Usual residence (complete dataset)				
Cairns and Hinterland	1133	581	51.3% (48.4%, 54.2%)	Base
Cape York	220	120	54.5% (47.9%, 61.2%)	0.385
Torres and Northern Peninsula Area	443	275	62.1% (57.5%, 66.6%)	<0.001*
SEIFA category[1] (complete dataset)				
SEIFA 1 or 2	1276	719	56.3% (53.6%, 59.1%)	0.008*
SEIFA 3–10	520	257	49.4% (45.1%, 53.7%)	
Teenage mother	376	230	61.2% (56.2%, 66.1%)	0.003*
Antenatal Care 5 visits or more[1] (complete dataset), n = 1417 (78.9%)	1417	770	54.3% (51.7%, 56.9%)	0.996
Smoking this pregnancy[1] (1791 records—5 missing)	1022	567	55.5% (52.4%, 58.5%)	0.259
Body mass index categories[2] (all ages—1675 measures—121 missing)[1]				
Under weight (5.4%)	90	59	65.5% (55.5%, 75.6%)	0.152
Healthy weight (36.7%)	615	354	57.6% (53.6%, 61.5%)	Base
Over weight (26.0%)	436	233	53.4% (48.7%, 58.1%)	0.185
Obese (31.9%)	534	246	46.1% (41.8%, 50.3%)	<0.001*
Glucose tolerance				
Pre-existing diabetes[1] (1239 pathology measures—557 missing)	75	45	60.0% (48.7%, 71.3%)	0.390
Gestational diabetes[1] (793 pathology measures—1003 missing)	141	77	54.6% (46.3%, 62.9%)	0.595
Pregnancy-induced hypertension[1] (complete dataset)	92	58	63.0% (53.0%, 73.1%)	0.087
Nutrient status before/during cohort pregnancy				
Ever iron deficient during cohort pregnancy[1] (1133 pathology measures—663 missing)	672	452	67.3% (63.7%, 70.8%)	<0.001*
Ever iron deficient before cohort pregnancy (561 pathology measures)	324	224	69.1% (64.1%, 74.2%)	<0.001*
Low red cell folate before/during cohort pregnancy[1] (376 pathology measures—1420 missing), n = 66 (17.6%)	66	44	66.7% (55.0%, 78.3%)	0.785
Low B12 before/during cohort pregnancy[1] (328 pathology measures–1468 missing), n = 63 (19.2%)	63	48	76.2% (65.4%, 87.0%)	0.202

[1] Information on number of missing values provided for those variables used for multivariable analysis.
[2] Criteria for body mass index categories for adults applied for mothers aged 18 years and older, and age-based criteria for mothers younger than 18 years (where available, n = 1675).
* *P*-value less than 0.05.

following variables: anaemia during pregnancy, pregnancy induced hypertension, ethnicity, age, SEIFA index and antenatal care received. Twenty imputed datasets were created for each cohort. Multivariable general linear models for the binomial family using the log link to estimate RRs were used to identify independent risk factors for anaemia during pregnancy for imputed data.

Results of multivariable models for complete case and imputed data analyses are presented as RRs and 95% CIs. *P*-values of less than 0.05 were considered statistically significant. Analysis was conducted using Stata version 13 (StataCorp, Lakeway Drive, College Station, Texas).

Results

Data provided in May 2017 included information for 2332 mothers who gave birth to 2548 Aboriginal and Torres

Table 2 Prevalence of anaemia during the cohort pregnancy by characteristics of mothers, Cape York cohort

Characteristics of mothers (data available and data missing[1])	*Mothers (n)*	*Mothers with anaemia in cohort pregnancy (n)*	*Prevalence of anaemia in pregnancy, % (95% CI)*	P-*values (logistic regression)*
All	280	156	55.7% (49.9%, 61.6%)	n/a
Ethnicity[1] (complete dataset)				
Aboriginal	249	140	56.2% (50.0%, 62.4%)	Base
Torres Strait Islander, n = 16 (5.7%)[2]	16	—	—	0.335
Both Aboriginal and Torres Strait Islander, n = 15 (5.4%)[2]	15	—	—	0.775
Usual residence (complete dataset)				
Cairns and Hinterland	18	9	50.0% (24.4%, 75.6%)	Base
Cape York	261	146	55.9% (49.9%, 62.0%)	0.625
Torres and Northern Peninsula Area[2]	—	—	—	n/a
SEIFA category[1] (complete dataset)				
SEIFA 1 or 2	255	144	56.5% (50.3%, 62.6%)	0.81
SEIFA 3–10	25	12	48.0% (27.0%, 69.0%)	
Teenage mother	57	39	68.4% (56.0%, 80.9%)	0.032*
Antenatal Care 5 visits or more[1] (complete dataset)	251	137	54.6% (48.4%, 60.8%)	0.265
Smoking this pregnancy[1] (278 record—2 missing)	187	108	57.8% (50.6%, 64.9%)	0.257
Body mass index categories[3] (all ages 107 measures—173 missing)				
Under weight (23.4%)	25	14	56.0% (35.1%, 76.9%)	0.721
Healthy weight (35.5%)	38	23	60.5% (44.2%, 76.8%)	Base
Over weight (25.2%)[2]	27	—	↓	0.033*
Obese (15.9%)[2]	17	—	↓	—
Glucose tolerance[2]				
Pre-existing diabetes[1] (212 pathology measures—68 missing)	10	—	—	0.783
Gestational diabetes[1] (140 pathology measures—140 missing)	28	—	↓	0.006*
Pregnancy-induced hypertension[1] (complete dataset)[2]	2	—	—	0.097
Nutrient status (iron, folate, B12) before/during cohort pregnancy				
Ever iron deficient *during* cohort[1] pregnancy (136 pathology measures—144 missing)	54	34	63.0% (49.6%, 76.3%)	0.178
Ever iron deficient *before* cohort pregnancy (77 pathology measures—203 missing)	37	28	75.7% (61.2%, 90.2%)	0.022*
Low red cell folate *before/during* cohort pregnancy[1] (59 pathology measures—221 missing)[2]	—	—	—	0.443
Low B12 *before/during* cohort pregnancy[1] (51 pathology measures—229 missing)[2]	—	—	—	n/a

[1] Information on number of missing values provided for those variables used for multivariable analysis.
[2] Numbers too small to report are shown as —.
[3] Criteria for body mass index categories for adults applied for mothers aged 18 years and older, and age-based criteria for mothers younger than 18 years (where available, n = 107).
* *P*-value less than 0.05.

Strait Islander babies between 1 January 2006 and 31 December 2010 in Far North Queensland.

Exclusions: For the purpose of this report, non-Indigenous mothers (n = 15) and mothers normally resident outside of Far North Queensland (n = 29) were excluded. Births that were not the first birth in the cohort years were excluded (n = 289). Mothers with missing information for haemoglobin levels during pregnancy (n = 119) were also excluded. Following exclusions, the resultant dataset included information for 2076 Aboriginal and Torres Strait Islander mothers who gave birth to 2095 babies including 19 sets of twins, between 2006 and 2010 (Figure 2).

The 2009–2010 cohort: After exclusions there were 1796 mothers of whom half (50.7%) were Aboriginal, 36.4% Torres Strait Islander and 13.0% both Aboriginal and Torres Strait Islander (Table 1). More than half were normally resident in the Cairns and Hinterland Health Service District (63.1%), the remaining in Cape York (12.3%) or the Torres Strait and Northern Peninsula Area (24.7%) (Figure 1). Most mothers (71.1%) lived in localities with a SEIFA ranking in the lowest or second lowest decile.[22]

Table 3 Risk factors for anaemia during pregnancy—2009–2010 mothers (n = 1796): Multivariable analysis—complete case analysis and analysis with imputed data

	Complete case analysis (n = 1052)				*Imputed data analysis (n = 1796)*				
Characteristic	*Anaemia, n = 619 (58.8%)*	*No Anaemia, n = 433 (41.2%)*	*Relative risk (95% confidence interval)*	P-*value*	*Number of missing values (%)*	*Anaemia, n = 976 (54.3%)*	*No anaemia, n = 820 (45.7%)*	*Relative risk (95% confidence interval)*	P-*value*
Body mass index					121 (6.7%)				
Under weight	43 (7.0%)	20 (4.6%)	1.06 (0.88, 1.27)	0.533		66 (6.8%)	33 (4.0%)	1.10 (0.94, 1.29)	0.246
Healthy weight	255 (41.2%)	152 (35.1%)	1	–		391 (40.1%)	275 (33.5%)	1	–
Over weight	167 (27.0%)	114 (26.3%)	1.0 (0.89, 1.12)	0.971		253 (26.0%)	213 (26.0%)	0.97 (0.87, 1.08)	0.597
Obese	154 (24.9%)	147 (34.0%)	0.87 (0.76, 1.0)	0.049*		266 (27.2%)	299 (36.5%)	0.87 (0.77, 0.97)	0.013*
SEIFA category					nil				
SEIFA 1 and 2	468 (75.6%)	305 (70.4%)	1			719 (73.7%)	557 (67.9%)	1	
SEIFA 3–10	151 (24.4%)	128 (29.6%)	0.88 (0.78, 0.99)	0.033*		257 (26.3%)	263 (32.1%)	0.86 (0.78, 0.95)	0.003*
Mother was iron deficient during pregnancy					663 (36.9%)				
No	210 (33.9%)	222 (51.3%)	1			321 (32.9%)	423 (51.6%)	1	
Yes	409 (66.1%)	211 (48.7%)	1.34 (1.19, 1.50)	<0.001*		655 (67.1%)	397 (48.4%)	1.40 (1.23, 1.60)	<0.001*

Both models were adjusted for the confounding effect of age of mother (no missing values imputed). Imputed data are averages of 20 imputations.
* P-value less than 0.05.

Table 4 Risk factors for anaemia during pregnancy—Cape York mothers (n = 280): Multivariable analysis—complete case analysis and analysis with imputed data

	Complete cases analysis (n = 79)				*Imputed data analysis (n = 280)*				
Characteristic	*Anaemia, n = 33 (41.8%)*	*No Anaemia, n = 46 (58.2%)*	*Relative risk (95% confidence interval)*	P-*value*	*Number of missing values (%)*	*Anaemia, n = 156 (55.7%)*	*No Anaemia, n = 124 (44.3%)*	*Relative risk (95% confidence interval)*	P-*value*
Body mass index					173 (61.8%)				
Under weight	10 (30.3%)	6 (13.0%)	1.04 (0.63, 1.72)	0.869		55 (35.4%)	23 (18.8%)	1.07 (0.82, 1.39)	0.609
Healthy weight	14 (42.4%)	11 (23.9%)	1	—		64 (40.8%)	37 (29.6%)	1	—
Over weight	8 (24.2%)	16 (34.8%)	0.67 (0.35, 1.30)	0.238		27 (17.4%)	34 (27.7%)	0.74 (0.51, 1.07)	0.107
Obese	1 (3.0%)	13 (28.3%)	0.13 (0.02, 0.85)	0.034*		10 (6.4%)	30 (23.9%)	0.40 (0.19, 0.86)	0.019*

Both models were adjusted for the confounding effect of having had pre-existing diabetes or gestational diabetes (132 missing values imputed). Imputed data are averages of 20 imputations.
* P-value less than 0.05.

The mean age of mothers was 25.2 years (SD = 6.4) ranging from 13 up to 48 years. One in five mothers (21.0%) were teenagers. Median parity was two, ranging from 0 to 16. Most mothers (78.9%) had at least five antenatal healthcare visits in pregnancy. More than half (57.1%) smoked in pregnancy. Mean body mass index of the mothers aged 18 years and over (measurements available n = 1535) was 27.7 (6.6) ranging from 16.0 to 56 kg/m^2.

Among mothers with glucose tolerance results, 6.1% (n = 1239) had pre-existing diabetes and 17.8% (n = 794) had gestational diabetes. PDC records showed that 5.1% had pregnancy-induced hypertension. Among mothers with prior records of blood pressure 17.6% (n = 812), had hypertension. More than half of the mothers with measures of Ferritin had iron deficiency during (59.3%, n = 1133) or before (57.8%, n = 561) the cohort pregnancy.

The Cape York cohort: The majority (88.9%) of these mothers (n = 280) were Aboriginal and the remaining were Torres Strait Islander (5.7%) or both Aboriginal and Torres Strait Islander (5.4%) (Table 2). Nearly all (93.2%) were usually resident in Cape York, 6.4% in Cairns and Hinterland Health Service District and one mother in the Torres Strait and Northern Peninsula Area (Figure 1). Most (91.1%) mothers lived in localities with a SEIFA ranking in the lowest or second lowest decile.[22]

The mean age of these mothers was 25.0 years (SD = 6.4) ranging from 15 to 40 years. One in five (20.4%) were teenagers. Median parity was two, ranging from nil to eight.

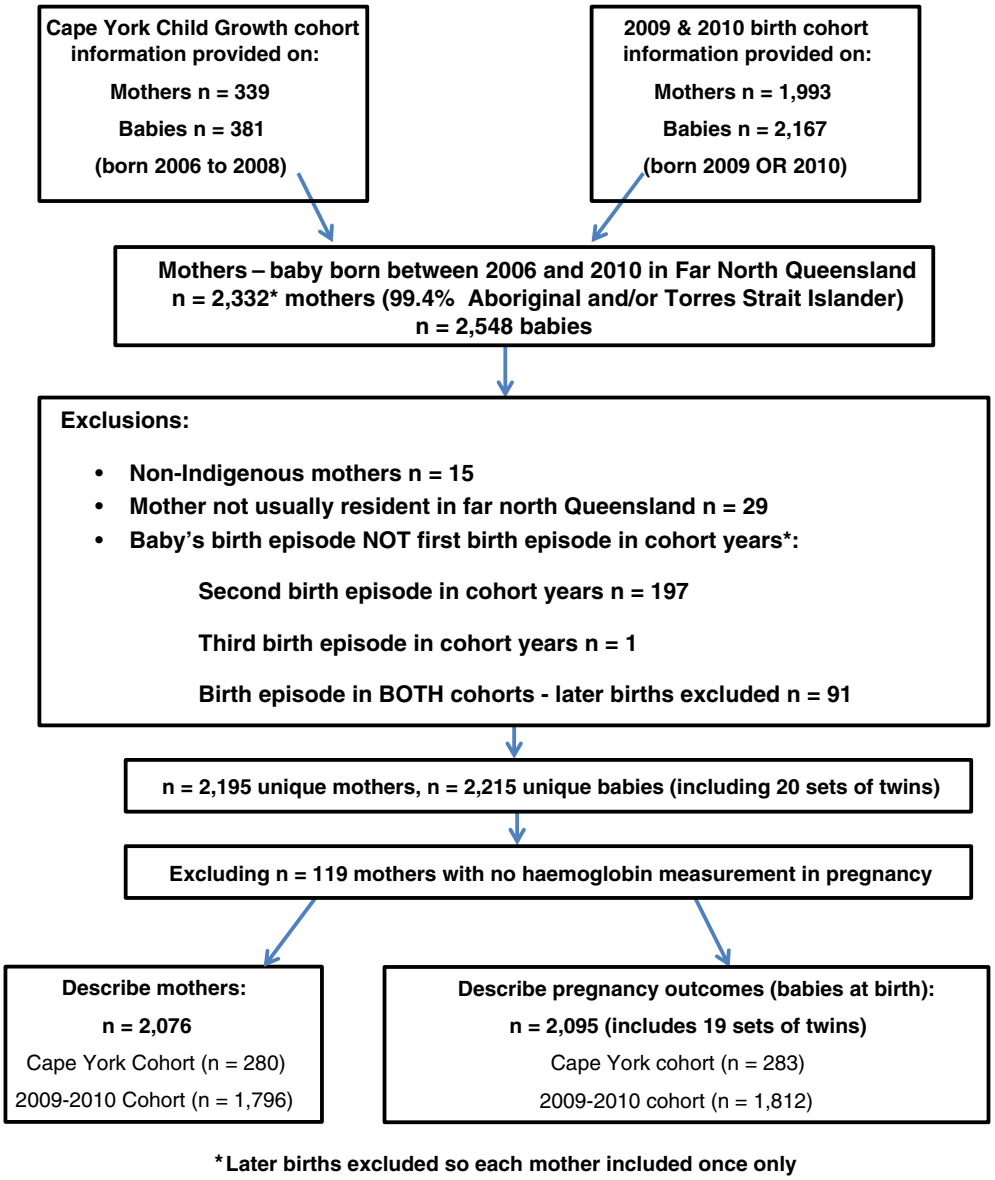

Figure 2 Flow chart: mothers and pregnancy outcomes showing study inclusions and exclusions.

Most mothers (89.6%) had at least five antenatal health-care visits in pregnancy. Many (67.3%) smoked in pregnancy. Mean body mass index of the mothers aged 18 years and over (measurements available n = 98) was 24.4 (5.8) ranging from 16.1 to 37.7 kg/m^2.

Where glucose tolerance results were available 4.7% (n = 212) had pre-existing diabetes and 20.0% (n = 140) had gestational diabetes. PDC records showed that 7.5% had pregnancy-induced hypertension. Among mothers with prior records of blood pressure, 20.6% (n = 272) had hypertension. Of those with measures of Ferritin, 39.7% (n = 54) had iron deficiency during the cohort pregnancy while 48.1% (n = 77) had iron deficiency before the cohort pregnancy.

2009–2010 cohort—Pregnancy outcomes: Among the 1812 babies born to these 1796 mothers, 53.9% were boys. Seventeen (0.9%) were still born and there were 10 (0.6%) neonatal deaths (Table S7). Among the liveborn babies (n = 1795), median gestational age at birth was 39 weeks, ranging from 22 to 42 weeks. Mean birthweight was 3240 g (SD = 649 g) ranging from 440 to 5430 g. About 1 in 10 babies were low birthweight (10.6%), premature (11.4%) or macrosomic (9.6%) (birthweight ≥ 4000 g).

Cape York cohort—Pregnancy outcomes: Among the 283 babies born to these 280 mothers, 51.9% were boys (Table S8). No information was available for perinatal mortality for this cohort. Median gestational age was 39 weeks, ranging from 27 to 42 weeks. Mean birthweight was 3097 g (SD = 591 g) ranging from 800 to 5320 g. About one in seven babies (13.8%) were low birthweight, 11.7% premature and some (4.6%) macrosomic (birthweight ≥ 4000 g).

Overall, more than half of the mothers (54.5% (95% CI: 52.4%, 56.7%)) had anaemia during pregnancy—2009 and 2010 birth cohort mothers: 54.3% (95% CI: 52.0%, 56.6%); Cape York Child Growth mothers: 55.7% (95% CI: 49.9%, 61.6%). There was no significant difference in prevalence of anaemia by cohort (P = 0.668). Compared to those not anaemic in pregnancy, mothers of the 2009-2010 cohort who had anaemia in pregnancy were younger (mean age 24.8 (24.4, 25.2) v 25.7 (25.3, 26.1) P =0.003, had lower mean BMI (27.0 (26.6, 27.4) v 28.4 (27.9, 28.9) P = <0.001), higher parity (median parity 2 (IQR 1, 4) v 2 (1, 3) P = 0.02) and lower Ferritin levels (anaemic mothers median Ferritin 14 (IQR 7,28) ug/L v non-anaemic mothers; 18.7 (10, 42) P = 0.039). Mothers with iron deficiency (P <0.001) and those living in socio-economically disadvantaged localities (p = 0.008) were more likely to have anaemia in pregnancy but mothers who were obese were less likely to have anaemia in pregnancy (P <0.001) (Table 1 and Table S5). Mothers with anaemia in pregnancy had babies with higher birth weights than babies of non-anaemic mothers (mean grams 3269 (95% CI 3230, 3308) v 3205 (3159, 3252) P = 0.038) and had fewer low birth weight babies (8.5% low birth weight babies (95% CI 6.9%, 10.4%) v 13.0% (10.9%, 15.5%) P = 0.002. No other differences were seen in pregnancy outcomes (Table S7). Compared to those not anaemic in pregnancy, Cape York mothers who had anaemia in pregnancy had lower mean BMI (22.3 (20.9, 23.7) v. 26.0 (24.3, 27.7) P = 0.002) and tended to be younger though the difference in age was not statistically significant (mean age 24.4 years (95% CI 23.4, 25.4) v. 25.9 (24.8, 27.0) P = 0.054). Mothers who were overweight (n = 9, P = 0.033) were less likely to be anaemic as were mothers with gestational diabetes (n = 7, P = 0.006) but the number of these mothers was small. No difference was seen in parity (anaemic mothers median parity 2 (IQR 1, 3) v 2 (1, 3) [P = 0.602). Similarly no difference was seen in Ferritin levels (anaemic mothers; median Ferritin 20.8 ug/L (IQR 10.3,47.8) v. 25.5 (15.3, 57.3) P = 0.589) but mothers with prior iron deficiency had more anaemia in pregnancy (P = 0.022) (Table 2 and Table S6). There were no differences in pregnancy outcomes for anaemic and non-anaemic Cape York mothers (Table S8). Results of bivariate comparisons of mothers with anaemia with those without, and their pregnancy outcomes, are shown in Tables S5–S8.

Multivariable analysis 2009–2010 cohort: After controlling for age, mothers who were iron deficient during pregnancy were more likely to be anaemic (RR: 1.40, P < 0.001) (Table 3; imputed data analysis). Mothers from relatively advantaged localities (SEIFA decile 3 and above) were less likely to be anaemic (RR: 0.86, P = 0.003), as were mothers who were obese (RR: 0.87, P = 0.013).

Cape York cohort: After controlling for existing or gestational diabetes, only body mass index remained statistically significant for these mothers (being obese: RR = 0.40, P = 0.019) (Table 4; imputed data analysis).

Discussion

Among the Aboriginal and Torres Strait Islander mothers of Far North Queensland described here, over half had anaemia in pregnancy (54.5%, n = 2076). This is much higher than among pregnant women elsewhere in Australia but similar to findings from two remote Northern Territory communities, where 50% of mothers had anaemia in pregnancy.[13] These results reflect the higher rates of anaemia reported among Australian Indigenous people in recent national health surveys.[25]

Although other conditions can cause anaemia, iron deficiency is the 'usual suspect' as the cause of anaemia in pregnancy.[15,26] Among the 2009 and 2010 birth mothers, for whom data were more complete, analysis confirmed that iron deficiency was strongly associated with anaemia in pregnancy.

Compared to the average Australian mother in 2016, the mothers described here were younger, more likely to smoke and they had less antenatal care.[27] The prevalence of obesity was higher among the 2009–2010 birth mothers, although not the Cape York mothers. About one in four of these Far North Queensland mothers had diabetes in pregnancy compared to about one in eight mothers Australia-wide in 2016.[27] Previous reports of the poor health and nutrition of young Indigenous women in North Queensland also flagged the potentially detrimental intergenerational effects.[28] The pregnancy outcomes reported here, with more premature and low birthweight babies, reflect the poor nutrition and health status of these mothers. The association of anaemia of mothers with increased birth

weight of the babies may reflect their marginal nutrition status, with the requirements of bearing a healthy weight baby depleting the limited nutritional reserves of these mothers.

An unexpected finding was that obese mothers were less likely to be anaemic than other mothers, though their rates of anaemia (46.1%) were still high. It may be that the higher food intake resulting in obesity provides a higher nutrient intake. However, maternal obesity is never recommended because of the negative health effects on the mother and her baby.[28] Instead, mothers need diets sufficiently nutritious to meet their requirements without excessive energy intakes.

There are limitations in this study, which used health service information recorded during provision of routine care. Some information of interest is not recorded on electronic data collections such as indicators of food insecurity or nutrient supplement use. Missing data for some key variables particularly in the early years was a limitation. Some measurements used in this analysis may have been available only for selected mothers if clinical protocols prescribed specific pathology tests for 'high risk' mothers. Examples include measurements of glucose tolerance and Ferritin levels. Because 'missing at random' is an assumption for multiple imputation where 'missing not at random' was suspected, respective characteristics were carefully analysed in alternative models.

Despite these limitations, the findings reported here are consistent with the high rates of anaemia among young Aboriginal and Torres Strait Islander children and pregnant women reported elsewhere in remote Australia.[7,13] A recent review has shown that food insecurity is associated with increased risk of anaemia among women and young children in high and low income countries.[29] Food insecurity and poor diet of Aboriginal and Torres Strait Islander people have been documented in remote settings in Australia.[30,31]

There is increasing evidence of the importance of a nutrient-rich diet in pregnancy, not only for the mother but for the physical health and cognitive development of her child.[1,32] A nutrient-rich diet helps prevents anaemia and provides many nutrients needed for health. For mothers on low incomes, high cost is a barrier to healthy eating especially in remote settings.[33] Mothers with low iron status in pregnancy can benefit from supplements—in addition to a healthy diet—but reaching those with highest needs is challenging.[34] Fortification of flour with folate appears to have been especially effective at reaching vulnerable population groups.[35] But iron is a nutrient with potential for harm so iron supplementation must be targeted to those with specific needs.[4]

Complementary interventions to improve food security, promote good nutrition, and provide targeted iron supplementation and/or fortification are needed, designed and implemented in partnership with the Aboriginal and Torres Strait Islander communities.[36] Also essential are the policy commitment and funding to develop, implement and evaluate these interventions.[37] To 'Close the Gap'[38] in the health, education and economic status of Aboriginal and Torres Strait Islander people in Far North Queensland compared to their non-Indigenous peers, these high rates of anaemia in pregnancy among Aboriginal and Torres Strait Islander mothers must be reduced.

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Conflict of interest

The authors affirm that they have no conflict of interest to declare.

Authorship

DL conceived the research, obtained the necessary approvals to secure the data required, conducted preliminary statistical analysis and prepared the first draft of this manuscript. FT assisted with data management and preparation, and contributed to statistical analysis. PB contributed to study design and guided and contributed to statistical analysis. RM and MM contributed to study design, and manuscript development and preparation.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Data collections used as information sources to describe rates of anaemia in pregnancy and health indicators among Aboriginal and Torres Strait Islander mothers in Far North Queensland

Table S2 Definitions of variables used to describe Aboriginal and Torres Strait Islander mothers and their pregnancy outcomes in Far North Queensland, between 2006 and 2010

Table S3 Number and percentage (%) of missing values for variables used for multivariable analysis for risk factors for anaemia in pregnancy for each cohort

Table S4 Assessment of 'Missing-ness': *P*-values are results of statistical tests correlating missing (yes/no) with cohort, outcome anaemia, variables with no missing values and with other missing variables

Table S5 Mothers 2009 – 2010 cohort - comparison of mothers with anaemia during the cohort pregnancy with mothers who did not have anaemia during this pregnancy: Bivariate analysis – logistic regression

Table S6 Cape York mothers - comparing mothers with anaemia during the cohort pregnancy with mothers who did not have anaemia during this pregnancy: Bivariate analysis – logistic regression

Table S7 Pregnancy outcomes - 2009–2010 births: comparing those babies whose mother had anaemia in pregnancy with those babies whose mother did not have anaemia in pregnancy - results based on 1812 babies of whom 1795 were live born babies: Bivariate analysis – logistic regression

Table S8 Pregnancy outcomes - Cape York births: comparing those babies whose mother had anaemia in pregnancy with those babies whose mother did not have anaemia in pregnancy (n = 283 - all babies live-born): Bivariate analysis – logistic regression

3.2 Supplementary Materials

Supplementary Table 3.1
Data collections used as information sources to describe rates of anaemia in pregnancy and health indicators among Aboriginal and Torres Strait Islander mothers in Far North Queensland.

Year commenced	Data Collection
1986	**Queensland Perinatal Data Collection (PDC):** Information on Queensland mothers and their babies is recorded at the time of birth on the Perinatal Data Collection, which commenced in Queensland in 1986. Information is collected on all live births in Queensland and on all stillbirths of at least 20 weeks gestation and/or at least 400g in weight. For this study, information was extracted in respect of births which occurred from 01 January 2006 to 31 December 2010.
1999	**Auslab:** Pathology Queensland provides pathology services to all Queensland Health facilities. Pathology test results are recorded on centralised electronic systems. The Auslab system, which commenced in 1999, was in use for this purpose during the timeframe of the current research. For this study, information relating to mothers from 01 January 2000 up to 31 December 2010 was extracted.
2001	**Ferret:** A centralised electronic patient information and recall system rolled out in health services in Far North Queensland from 2001 to 2006 (Figure 2.1). Ferret was used mainly by community health services in remote Aboriginal and Torres Strait Islander communities. Data recorded on Ferret includes information from routine adult health checks, antenatal and child health checks. For this study, information relating to mothers was extracted from the date of roll-out of Ferret (2001 to 2006 - Figure 2.1) up to 31 December 2010.

Supplementary Table 3.2
Definitions of variables used to describe Aboriginal and Torres Strait Islander mothers and their pregnancy outcomes in Far North Queensland, between 2006 and 2010.

	Characteristics of Mothers
Maternal age	Age of a mother in completed years at the time of the birth of her baby.[1]
Teenage mother	Mother was aged less than twenty years at the birth of her baby.[1]
Parity	As reported in the Queensland Perinatal Data Collection - number of previous pregnancies resulting in live births or stillbirths, excluding the current pregnancy.
Body Mass Index (BMI)	Weight in kilograms divided by (height^2 in metres).[3]
Implausible weight and/or height values	Guidelines are available to identify implausible BMI values for children under the age of five years[5] but no equivalent guideline was identified for adolescents or adults. Instead implausible weights and heights were identified based on information on weights and heights of participants of the National Nutrition Survey 1995.[6] In 1995, no participating girl aged 12 years or more weighed less than 35 kilograms or had a height measure less than 140cm and no participating girl/woman aged 16 years or more weighed less than 40 kilograms.[6] Among the mothers of these two cohorts, none had body weights reported of less than 35 kilograms. Four heights of less than 140cm and nine weights of less than 40 kilograms for girls/women aged 16 years or over, were replaced with missing values. At the National Nutrition Survey 1995, 0.1% of women had a height of 180cm to 190cm and 0.2% had a body weight of 130 kilograms or more. [6] Eight mothers had a height measurement 180cm and 190cm recorded which were replaced with missing vales. Eleven mothers had weights between 130 kg and 140 kg recorded. These values were considered plausible and retained.
Implausible Body Mass Index (BMI)	For women aged 18 years, the 3rd percentile of Body Mass Index for age is 17.2kg.[7] As 3% of the reference population have Body Mass Index less than 17.2%, the definition of implausible low value for BMI was taken to be less than 16. Ten BMI values from 14 up to 16 for mothers aged 18 years and over, were changed to missing. Two mothers under the age of 18 years had BMI values between 15 and 16 which below but close to the third percentile BMI for age and therefore considered plausible.[7]

	Characteristics of Mothers
Smoking in pregnancy	As reported in the Queensland Perinatal Data Collection – any smoking recorded before and/or after 20 weeks gestation was classified as 'smoking in pregnancy'.
	Maternal health and nutrition indicators
Body Mass Index categories: aged 18 years and over	BMI was categorised for mothers aged eighteen years and older, as defined by the Australian National Health and Medical Council (BMI < 18.5 underweight, 18.5 - <25.0 healthy weight, 25.0 - < 30.0 overweight, 30 or more obese).[3]
Body Mass Index categories: aged less than 18 years	For mothers less than eighteen years of age, BMI was classified into the same categories (underweight, healthy weight, overweight, obese) using the criteria for girls aged between 2 years and eighteen years developed by Cole et al.[8, 9] These criteria have been used for child and adolescent participants of recent national surveys in Australia - the 2011-12 Australian National Health survey and the 2012-13 Australian Aboriginal and Torres Strait Islander Health survey and are the criteria recommended for analysis of survey data in the National Health Dictionary.[10, 11 2]
Iron deficiency	Defined as recommended by Pasricha et al. as Ferritin <15ug/L.[12] Ferritin levels are raised in the presence of infection and/or inflammation however insufficient information was available to adjust for inflammation (transferrin saturation, C-reactive protein). Consequently Ferritin levels >=15ug/L were classified as normal.
Pre-existing Diabetes	Diabetes defined using criteria as specified by the International Association of Diabetes and Pregnancy Study Groups, and by Queensland Health: fasting glucose levels of 7 mmol/L or more and/or glycated haemoglobin (hbA1c) levels of 6.5% or more. Diabetes was considered to be **'pre-existing'** if a positive test result was reported before or during pregnancy. [4 13 14]
Gestational diabetes	Among mothers without pre-existing diabetes, gestational diabetes was defined as specified by the International Association of Diabetes and Pregnancy Study Groups[13] - glucose tolerance test results: fasting glucose of 5.1 mmol/L up to 7mmol/L , or one hour glucose 10.0 mmol/L or more, or two hour glucose 8.5 mmol/L or more.[4, 13]
Low Folate	Defined as per Queensland Health Pathology - measurement result <356 nmol/L[15]

	Characteristics of Mothers
Low Vitamin B12	Defined as per Queensland Health Pathology - measurement result less than <133 pmol/L.[15]
Hypertension	Defined as per Gabb et al. and by Queensland Health - systolic blood pressure equal to or greater than 140mm Hg and/or diastolic blood pressure equal to or greater than 90mm Hg[14, 16, 17]
	Pregnancy outcomes
L**ive born**	Baby with gestational age of at least 20 weeks or at least 400g birth weight, shows signs of life at birth.[1]
Stillborn	Baby of at least twenty weeks gestational age or 400g or less birth weight, who died before completed birth. [1]
Neonatal death	Death before age 28 days of a live born baby.[1]
Perinatal death	Baby is stillborn or dies in the neonatal period.[1]
Gestational age at birth	Best clinical estimate of duration of pregnancy at birth, expressed in completed weeks[2]
P**rematurity**	Gestational age at birth of less than 37 weeks [18, 19]
Low birth weight	Birth weight of a live born baby less than 2,500g [18]
Macrosomia	Birth weight of 4,000g or more[18]
High Macrosomia	Birth weight of 4,500g or more.[18]

Footnotes:

Unless otherwise stated, definitions are those used by the Australian Institute of Health and Welfare, the National Perinatal Data Collection and/or the National Health and Medical Research Council [1 2 3]

Measurement sources: Values for the different variables are as recorded on the respective data collection systems. These electronic systems do not hold information to indicate where the values recorded were self-reported by mothers or the results of measurements by clinicians. Most results reported here are based on measurements made as prescribed by protocols for routine antenatal care.[4] Results of oral glucose tolerance tests and measurements of nutrient status – iron, folate, vitamin B12 - are the results of pathology laboratory measurements.

Supplementary Table 3.2 References

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Supplementary Table 3.3
Number and percentage (%) of missing values for variables used for multivariable analysis for risk factors for anaemia in pregnancy for each cohort.

Variable	**2009-2010 cohort (total n = 1796) missing n (%)**	**Cape York cohort (total n = 280) missing n (%)**
Ethnicity	nil	nil
Maternal age	nil	nil
Body Mass Index category	121 (6.7%)	173 (61.8%)
Parity	505 (28.1%)	83 (29.6%)
SEIFA for residence of mother	nil	nil
Smoking during pregnancy	5 (0.3%)	2 (0.7%)
5 or more antenatal visits	nil	nil
Pregnancy induced hypertension	nil	nil
Pre-existing Diabetes	557 (31.0%)	68 (24.3%)
Gestational Diabetes	1003 (55.8%)	140 (50.0%)
Low RCF before or during pregnancy	1420 (79.1%)	221 (78.9%)
Low B12 before and during pregnancy	1468 (81.7%)	229 (81.8%)
Iron deficiency during pregnancy	663 (36.9%)	144 (51.4%)
Birth weight of baby	1 (0.06%)	nil

Supplementary Table 3.4

Assessment of "Missing-ness": p-values are results of statistical tests correlating missing (yes/no) with cohort, outcome anaemia, variables with no missing values, and with other missing variables.

	Birth weight	**Smoking**	**DM**	**GDM**	**Hypertension**	**RCF**	**B12**	**BMI**	**Iron**	**Parity**
Missing values	1 (1; 0)	7 (5; 2)	625 (557; 68)	1143 (1003; 140)	1264 (1256; 8)	1641 (1420; 221)	1697 (1468; 229)	294 (121; 173)	807 (663; 144)	588 (505; 83)
Cohort	P=1.0	P=0.241	P=0.025*	P=0.071	P<0.001*	P=0.937	P=1.0	P<0.001*	P<0.001*	P=0.618
			C1 More		Almost all in C1			Many More in C2	More in C2	
Anaemia	P=1.0	P=0.466	P=0.471	P=0.425	P=0.007*	P<0.001*	P<0.001*	P<0.001*	P<0.001*	P=0.171
	P=1.0	P=1.0	P=0.282	P=0.086	P=0.005*	P<0.001*	P<0.001*	P=0.001*	P<0.001*	P=0.317
	NA*	P=0.505	P=0.403	P=0.041*	P=0.736	P=0.142	P=0.044*	P=0.010*	P=1.0	P=0.237
				Anaem More C2	Anaem Less C1	Anaem Less C1	Anaem Less	Anaem More	Anaem Less in C1	
PIH	P=1.0	P=1.0	P=0.246	P=0.244	P=0.137	P=0.554	P=0.452	P=0.781	P=0.921	P<0.001
	P=1.0	P=1.0	P=0.355	P=0.281	P=0.243	P=0.693	P=0.491	P=0.670	P=0.825	P<0.001
	NA	P=1.0	P=0.792	P=1.0	P=0.114	P=0.781	P=0.775	P=0.170	P=0.258	P=0.080
										PIH More

	Birth weight	Smoking	DM	GDM	Hypertension	RCF	B12	BMI	Iron	Parity
Ethnicity	P=1.0	P=0.455	P<0.001*	P<0.001*	P<0.001*	P<0.001*	P=0.004*	P<0.001*	P<0.001*	P=0.075
	P=1.0	P=0.449	P<0.001*	P<0.001*	P<0.001*	P<0.001*	P=0.003*	P<0.001*	P<0.001*	P=0.033*
	NA	P=1.0	P=0.368	P=0.004*	P=1.0	P=0.777	P=0.608	P=0.698	P=0.075	P=0.187
			TSI Less in C1	TSI Less	TSI Less C1	TSI Less C1	TSI Less C1	TSI Less C1	TSI More C1	TSI Less C1
Age	NA	P=0.781	P<0.001*	P=0.007*	P=0.985	P=0.012*	P=0.071	P=0.420	P=0.072	P<0.001*
	NA	P=0.775	P<0.001*	P=0.081	P=0.871	P=0.015*	P=0.022*	P=0.956	P=0.033*	P<0.001*
	NA	P=0.322	P<0.001*	P=0.003*	P=0.527	P=0.465	P=0.386	P=0.297	P=0.7488	P<0.001*
			Young More	Young More		Young More C1	Young More C1		Older More C1	Young More
SEIFA	P=1.0	P=0.201	P<0.001*	P<0.001*	P<0.001*	P<0.001*	P<0.001*	P<0.001*	P<0.001*	P=0.223
	P=1.0	P=0.330	P<0.001*	P<0.001*	P<0.001*	P<0.001*	P<0.001*	P=0.003*	P<0.001*	P=0.203
	NA	P=1.0	P=0.051	P=0.003*	P=1.0	P=0.616	P=1.0	P=0.527	P=0.096	P=0.820
			Poor More in C1; in C2 reverse	Poor More in C1; in C2 reverse	Poor More in C1	Poor More in C1	Poor More in C1	Poor Less in C1	Poor More	

	Birth weight	Smoking	DM	GDM	Hypertension	RCF	B12	BMI	Iron	Parity
Antenatal care	P=1.0	P=0.142	P<0.001*	P<0.001*	P<0.001*	P=0.416	P=0.198	P=0.113	P=0.001*	P=0.003*
	P=1.0	P=0.066	P<0.001*	P<0.001*	P<0.001*	P=0.201	P=0.052	P<0.001*	P<0.001*	P=0.006*
	NA	P=1.0	P=0.177	P=0.239	P=1.0	P=0.226	P=0.074	P=0.429	P=0.030*	P=0.390
			No ANC More in C1	No ANC More in C1	No ANC More in C1			No ANC More in C1	No ANC More in C1; Less in C2!	No ANC Less
Missing by missing										
Smoking	P=1.0	/								
	P=1.0									
	NA									
DM	P=0.301	P=0.436	/							
	P=0.310	P=0.176								
	NA	P=1.0								
GDM	P=1.0	P=0.138	P<0.001*	/						
	P=1.0	P=0.071	P<0.001*							
	NA	P=1.0	P<0.001*							
			All M with M							

	Birth weight	Smoking	DM	GDM	Hypertension	RCF	B12	BMI	Iron	Parity
Hypertension	P=1.0	P=1.0	P<0.001*	P<0.001*	/					
	P=1.0	P=1.0	P<0.001*	P<0.001*						
	NA	P=1.0	P=0.101	P=0.282						
			M with M in C1	M with M in C1						
RCF	P=1.0	P=0.642	P<0.001*	P<0.001*	P<0.001*	/				
	P=1.0	P=0.282	P<0.001*	P<0.001*	P<0.001*					
	NA	P=1.0	P=0.865	P=0.379	P=0.210					
			M with M in C1	M with M in C1	M with M in C1					
B12	P=1.0	p=1.0	P<0.001*	P=0.001*	P<0.001*	P<0.001*	/			
	P=1.0	P=1.0	P<0.001*	P<0.001*	P<0.001*	P<0.001*				
	NA	P=1.0	P=0.208	P=0.121	P=0.358	P<0.001*				
			M with M in C1	M with M in C1	M with M in C1	M with M				

	Birth weight	Smoking	DM	GDM	Hypertension	RCF	B12	BMI	Iron	Parity
BMI	P=0.142	P<0.001*	P=0.451	P=0.008*	P<0.001*	P=0.063	P=0.022*	/		
	P=0.067	P<0.001*	P=0.478	P=0.129	P=0.758	P=0.020*	P=0.038*			
	NA	P=0.526	P=0.002*	P<0.001*	P=0.160	P=0.763	P=0.110			
		M with M	M with M in C2	M with M in C2	M not with M (confounding)	M not with M in C1	M not with M in C1			
Iron	P=0.389	P=0.016*	P<0.001*	P<0.001*	P=0.268	P<0.001*	P<0.001*	P=0.002*	/	
	P=0.369	P=0.065	P<0.001*	P<0.001*	P=0.394	P<0.001*	P<0.001*	P=0.382		
	NA	P=0.499	P=0.889	P=0.550	P=0.067	P<0.001*	P=0.002 *	P=0.028*		
			M with M in C1	M with M in C1		M with M	M with M in C1	M with M in C2		
Parity	P=1.0	P=1.0	P<0.001*	P=0.087	P=0.135	P<0.001*	P<0.001*	P=0.944	P=0.251	/
	P=1.0	P=0.624	P<0.001*	P=0.017*	P=0.086	P=0.001*	P<0.001*	P=0.917	P=0.192	
	NA	P=1.0	P<0.001*	P=0.191	P=0.053	P=0.038*	P=0.179	P=1.0	P=1.0	
			M with M	M not with M in C1		M with M	M with M in C1			

Foototes

First p-value relates to comparison for both cohorts combined; second p-value for comparison within cohort 1; third p-value for comparison within cohort 2.
p-values are results of exact Fisher's tests and t-tests; * p value less than 0.05
NA = not available
C1 = 2009 and 2010 birth cohort, C2 = Cape York mothers

Supplementary Table 3.5

Mothers 2009 – 2010 cohort - comparison of mothers with anaemia during the cohort pregnancy with mothers who did not have anaemia during this pregnancy: Bivariate analysis – logistic regression.

Ethnicity[(a)] (complete data set)	**All mothers n = 1796**	**Mother anaemic during cohort pregnancy n = 976 (54.3%)**	**Mother not anaemic during cohort pregnancy n = 820 (45.7%)**	**P-values**
Aboriginal	910 (50.7%)	493 (50.5%)	417 (50.9%)	base
Torres Strait Islander	653 (36.4%)	363 (37.2%)	290 (35.4%)	p = 0.58
Both Aboriginal and Torres Strait Islander	233 (13.0%)	120 (12.3%)	113 (13.8%)	p = 0.465
Usual Residence				
Cairns and Hinterland	1133 (63.1%)	581 (59.5%)	552 (67.3%)	base
Cape York	220 (12.3%)	120 (12.3%)	100 (12.2%)	p = 0.385
Torres and Northern Peninsula Area (NPA)	443 (24.7%)	275 (28.2%)	168 (20.5%)	p < 0.001*
SEIFA category[(a)] (complete data set)				
SEIFA 1 or 2	1276 (71.1%)	719 (73.7%)	557 (67.9%)	p = 0.008*
SEIFA 3 to 10	520 (29.0%)	257 (26.3%)	263 (32.1%)	

Ethnicity[a] (complete data set)	**All mothers n = 1796**	**Mother anaemic during cohort pregnancy n = 976 (54.3%)**	**Mother not anaemic during cohort pregnancy n = 820 (45.7%)**	**P-values**
Mothers' age at cohort birth[a] (complete data set) Years mean (SD)	25.2 (6.4) [13 – 48]	24.8 (6.4) [13 – 48]	25.7 (6.3) [14 – 44]	P = 0.003*
Teenage mother (<20years)	376 (21.0%)	230 (23.6%)	146 (17.8%)	p = 0.003*
Parity[a] median (IQR) n = 1291 (missing n = 505)	2 (1, 4) [0 - 16]	2 (1, 4) [0 - 10]	2 (1, 3) [0 - 16]	p = 0.020*
Antenatal Care 5 visits or more[a] (complete data set)	1417 (78.9%)	770 (78.9%)	647 (78.9%)	p = 0.996
Smoking this pregnancy[a] n = 1791 (missing n = 5)	1022 (57.1%)	567 (58.3%)	455 (55.6%)	p = 0.259
Body Mass Index[b] (BMI) (kg/m2) (18 years or older) mean (SD) n = 1535	27.7 (6.6) [16.0 – 56.0]	27.0 (6.3) [16.2- 56.0]	28.4 (6.8) [16.0 - 54.8]	p < 0.001*

Ethnicity[(a)] **(complete data set)**	**All mothers n = 1796**	**Mother anaemic during cohort pregnancy n = 976 (54.3%)**	**Mother not anaemic during cohort pregnancy n = 820 (45.7%)**	**P-values**
Body Mass Index categories[c] **(all ages)** n = 1675 (missing n = 121)(a)				
Under weight	90 (5.4%)	59 (6.6%)	31 (4.0%)	p = 0.152
Healthy weight	615 (36.7%)	354 (39.7%)	261 (33.3%)	*base*
Over weight	436 (26.0%)	233 (26.1%)	203 (25.9%)	p = 0.185
Obese	534 (31.9%)	246 (25.6%)	288 (36.8%)	p < 0.001*
Glucose Tolerance				
Pre-existing Diabetes[(a)] n =1239 (missing n = 557)	75 (6.1%)	45 (6.6%)	30 (5.4%)	p = 0.390
Gestational Diabetes[(a)] n = 793 (missing n = 1003)	141 (17.8%)	84 (16.2%)	85 (20.5%)	p = 0.595
Hypertension				
Hypertension - Ferret prior record blood pressure n = 812	143 (17.6%)	45 (14.0%)	42 (19.2%)	p = 0.111
Pregnancy Induced Hypertension[(a)] - PDC record **(complete data set)**	92 (5.1%)	58 (5.9%)	34 (4.2%)	p = 0.087

Ethnicity[a] (complete data set)	**All mothers n = 1796**	**Mother anaemic during cohort pregnancy n = 976 (54.3%)**	**Mother not anaemic during cohort pregnancy n = 820 (45.7%)**	**P-values**
Nutrient status before/during cohort pregnancy				
Ever iron deficient **during** cohort pregnancy[a] n = 1133 (missing n = 663)	672 (59.3%)	452 (66.5%)	220 (48.6%)	p < 0.001*
Ever iron deficient **before** cohort pregnancy n = 561	324 (57.8%)	224 (63.8%)	100 (47.6%)	p < 0.001*
Ferritin in pregnancy median ug/L (n = 1133) (IQR) (range)	16 (8, 34) [2 - 608]	14 (7, 28) [2 - 608]	18.7 (10, 42) [3 - 589]	p = 0.039*
Low Red Cell Folate **before/during** cohort pregnancy[a] n= 376 (missing n = 1420)	66 (17.6%)	44 (17.4%)	22 (18.3%)	p = 0.785
Low B12 **before/during** cohort pregnancy[a] n= 328 (missing n = 1468)	63 (19.2%)	48 (21.1%)	15 (15.0%)	p = 0.202

Footnotes:

Unless otherwise stated all values refer to absolute and relative frequencies n (%)

[a] Information on number of missing values provided for those variables used for multivariable analysis

[b]shown for mothers aged 18 years and over only (where available, n = 1535) as under aged 18 years, Body Mass Index can be interpreted only with information in respect of age.

[c]criteria for BMI categories for adults applied for mothers aged 18 years and older, and age-based criteria for mothers younger than 18 years (where available, n = 1675)

* p value less than 0.05

Supplementary Table 3.6

Cape York mothers - comparing mothers with anaemia during the cohort pregnancy with mothers who did not have anaemia during this pregnancy: Bivariate analysis – logistic regression.

Ethnicity[(a)] **(complete data set)**	**All mothers** **n = 280**	**Mother anaemic during cohort pregnancy** **n = 156 (55.7%)**	**Mother not anaemic during cohort pregnancy** **n = 124 (44.3%)**	**P-values**
Aboriginal	249 (88.9%)	140 (89.7%)	109 (87.9%)	base
Torres Strait Islander	16 (5.7%)	-	-	p = 0.335
both Aboriginal and Torres Strait Islander	15 (5.4%)	-	-	p = 0.775
Usual Residence				
Cairns and Hinterland	18 (6.4%)	-	-	base
Cape York	261 (93.2%)	146 (93.6%)	115 (92.7%)	p = 0.625
Torres and Northern Peninsula Area (NPA)	-	-	-	n/a
SEIFA category[(a)] **(complete data set)**				
SEIFA 1 or 2	255 (91.1%)	144 (92.3%)	111 (89.5%)	P = 0.81
SEIFA 3 to 10	25 (8.9%)	12 (7.7%)	13 (10.5%)	

Ethnicity[(a)] **(complete data set)**	**All mothers n = 280**	**Mother anaemic during cohort pregnancy n = 156 (55.7%)**	**Mother not anaemic during cohort pregnancy n = 124 (44.3%)**	**P-values**
Mothers' age at cohort birth[(a)] **(complete data set)** years mean (SD)	25.0 (6.4) [15 – 41]	24.4(6.4) [15 – 40]	25.9 (6.2) [16 – 41]	P = 0.054
Teenage mother (<20years)	57 (20.4%)	39 (25.0%)	18 (14.5%)	P = 0.032*
Parity median (IQR) n = 197 (missing n = 83)[(a)]	2 (1, 3) [0 - 8]	2 (1, 3) [0 - 6]	2 (1, 3) [0 - 8]	p = 0.602
Antenatal Care 5 visits or more[(a)] **(complete data set)**	251 (89.6%)	137 (87.8%)	114 (91.9%)	p = 0.265
Smoking this pregnancy[(a)] n = 278 (missing n = 2)	187 (67.3%)	108 (70.1%)	79 (63.7%)	p = 0.257
Body Mass Index[(b)] **(BMI)** (kg/m2) (18 years or older) mean (SD) range n = 98	24.4 (5.8) [16.1 - 37.7]	22.3 (4.6) [16.4 - 31.6]	26.0 (6.2) [16.1 - 37.7]	p = 0.002*

Ethnicity[a] **(complete data set)**	**All mothers n = 280**	**Mother anaemic during cohort pregnancy n = 156 (55.7%)**	**Mother not anaemic during cohort pregnancy n = 124 (44.3%)**	**P-values**
Body Mass Index categories[c] **(all ages)** n = 107 (missing n = 173) [a]				
Under weight	25 (23.4%)	14 (28.6%)	11 (19.0%)	p = 0.721
Healthy weight	38 (35.5%)	23 (46.9%)	15 (25.9%)	*base*
Over weight	27 (25.2%)	- ↓	-	p = 0.033*
Obese	17 (15.9%)	- ↓	-	p = 0.006*
Glucose Tolerance				
Pre-existing Diabetes[a] n =212(missing n = 68)	10 (4.7%)	-	-	p = 0.783
Gestational Diabetes[a] n =140 (missing n = 140)	28 (20.0%)	- ↓	-	p = 0.006*

Ethnicity[(a)] **(complete data set)**	**All mothers** **n = 280**	**Mother anaemic during cohort pregnancy** **n = 156 (55.7%)**	**Mother not anaemic during cohort pregnancy** **n = 124 (44.3%)**	**P-values**
Hypertension				
Hypertension - Ferret prior record blood pressure n = 272	56 (20.6%)	33 (21.7%)	23 (19.2%)	p = 0.607
Pregnancy Induced Hypertension[(a)] – PDC record (complete data set)	21 (7.5%)	-	-	p = 0.097
Nutrient status (Iron, folate, B12) before/during cohort pregnancy				
Ever iron deficient **during** cohort[(a)] pregnancy n =136 (missing n = 144)	54 (39.7%)	34 (44.7%)	20 (33.3%)	P = 0.178
Ever iron deficient **before** cohort pregnancy n = 77	37 (48.1%)	- ↑	-	p = 0.022*
Ferritin in pregnancy median ug/L (IQR) n = 136	23.8 (13, 53.4) [3, 543]	20.8 (10.3, 47.8) [3, 543]	25.5 (15.3, 57.3) [4 - 469]	p = 0.589

Ethnicity[a] **(complete data set)**	**All mothers** **n = 280**	**Mother anaemic during cohort pregnancy** **n = 156 (55.7%)**	**Mother not anaemic during cohort pregnancy** **n = 124 (44.3%)**	**P-values**
Low Red Cell Folate **before/during** cohort pregnancy[a] n= 59 (missing n = 221)	6 (10.2%)	-	-	p = 0.443
Low B12 **before/during** cohort pregnancy[a] n= 51 (missing n = 229)	5 (9.8%)	-	-	n/a

Footnotes:

Unless otherwise stated all values refer to absolute and relative frequencies n (%)
[a]Information on number of missing values provided for those variables used for multivariable analysis
[b] Shown for mothers aged 18 years and over only (where available, n = 98) as under aged 18 years, Body Mass Index can be interpreted only with information in respect of age.
[c] Criteria for BMI categories for adults applied for mothers aged 18 years and older, and age-based criteria for mothers younger than 18 years (where available, n = 107) (see Supplementary Table 3.2 for further details)
- numbers too small to report
* p value less than 0.05

Supplementary Table 3.7

Pregnancy outcomes - 2009-2010 births: comparing those babies whose mother had anaemia in pregnancy with those babies whose mother did not have anaemia in pregnancy - results based on 1812 babies of whom 1795 were live born babies: Bivariate analysis – logistic regression.

Pregnancy outcomes	**All babies n =1812**	**Mother was anaemic during pregnancy n = 982 (54.2%)**	**Mother not anaemic during pregnancy n = 830 (45.8%)**	**P-value**
Male	976 (53.9%)	512 (52.1%)	464 (55.9%)	p = 0.114
Twin	32 (1.8%)	12 (1.2%)	20 (2.4%)	p = 0.061
Still born	17 (0.9%)	-	-	p = 0.544
Neonatal deaths[(a)]	10 (0.6%)	-	-	p = 0.371
Caesarean birth[(a)]	447 (24.9%)	247 (25.4%)	200 (24.4%)	p = 0.624
Gestational age at birth weeks[(a)] median (IQR)	39 (38, 40) [22 - 42]	39 (38, 40) [22 - 42]	39 (38, 40) [22 - 42]	p = 0.113
Premature[(a)]	205 (11.4%)	108 (11.1%)	97 (11.8%)	p = 0.630
Birth Weight[(a)] grams[(b)] mean (SD) (missing n = 1)	3240 (649) [440 - 5430]	3269 (621) [440 - 5430]	3205 (679) [495 - 5050]	p = 0.038*

Pregnancy outcomes	All babies n =1812	Mother was anaemic during pregnancy n = 982 (54.2%)	Mother not anaemic during pregnancy n = 830 (45.8%)	P-value
Birthweight categories[(a)] **n (%)**				
Low birth weight <2,500g	190 (10.6%)	83 (8.5%)	107 (13.0%)	p = 0.002*
Normal birth weight 2,500 - <4,000g	1433 (79.8%)	795 (81.6%)	638 (77.7%)	base
Macrosomic >=4,000g	172 (9.6%)	96 (9.9%)	76 (9.3%)	p = 0.933

Footnotes:

unless otherwise stated all values refer to absolute and relative frequencies n (%)
[(a)]Live born babies only n = 1795
[(b)] Birth Weight included in multivariable analyses
- numbers too small to report
* signifies p value less than 0.05

Supplementary Table 3.8

Pregnancy outcomes - Cape York births: comparing those babies whose mother had anaemia in pregnancy with those babies whose mother did not have anaemia in pregnancy (n = 283 - all babies live-born): Bivariate analysis – logistic regression.

	All babies n =283	**Mother was anaemic during pregnancy n =157 (55.5%)**	**Mother not anaemic during pregnancy n = 126 (44.5%)**	p value
Pregnancy outcomes				
Male	147 (51.9%)	82 (52.2%)	65 (51.6%)	p = 0.914
Twin	-	-	-	p = 0.286
Caesarean birth	93 (32.8%)	48 (30.6%)	45 (35.7%)	p = 0.295
Gestational age at birth weeks median (IQR)	39 (38, 40) [27 - 42]	39 (38, 40) [30 - 42]	39 (38, 40) [27, 41]	p = 0.461
Premature	33 (11.7%)	18 (11.5%)	15 (11.9%)	p = 0.909
Birth weight grams[(a)] mean (SD) range (complete data set)	3097 (591) [800 - 5320]	3084 (590) [1360 - 5300]	3114 (594) [800 - 5320]	p = 0.677

	All babies n =283	Mother was anaemic during pregnancy n =157 (55.5%)	Mother not anaemic during pregnancy n = 126 (44.5%)	p value
Birth weight categories				
Low birth weight <2,500g	39 (13.8%)	26 (16.6%)	13 (10.3%)	p = 0.122
Normal birth weight 2,500 - <4,000g	231 (81.6%)	123 (78.3%)	108 (85.7%)	base
Macrosomic >=4,000g	13 (4.6%)	-	-	p = 0.561

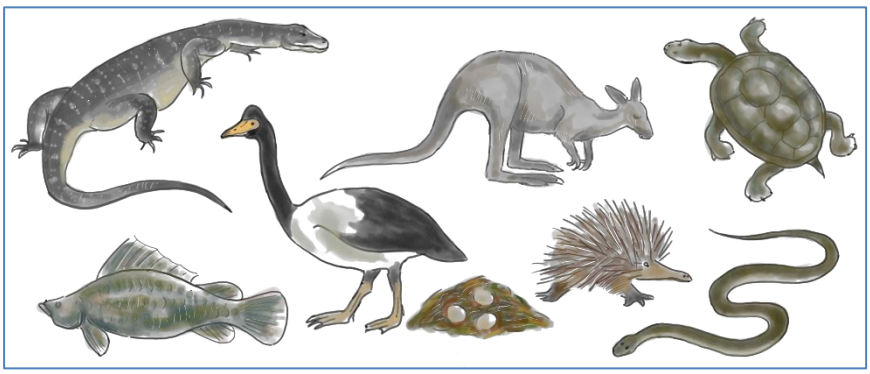
Footnotes:
unless otherwise stated all values refer to absolute and relative frequencies n (%)
[(a)]Birth Weight included in multivariable analyses
- numbers too small to report
* signifies p value less than 0.05

Foreword Chapter 4 (Results 2)

In the preceding chapter, I described anaemia in pregnancy among the mothers included in this research. In Chapter 4, I present results of this research in respect of the children. The information here describes the incidence of anaemia at age 6-23 months among children of the remote Aboriginal and Torres Strait Islander communities of Far North Queensland and the risk factors for early childhood anaemia among these children. Together Chapter 3 and Chapter 4 describe anaemia in the first thousand days of life among Aboriginal and Torres Strait Islander children in Far North Queensland.

This information presented in this chapter was published in the *Australian and New Zealand Journal of Public Health* in June 2019;

Anaemia in Early Childhood D, Buttner P, Thompson F, Makrides M, McDermott R. Anaemia in early childhood among Aboriginal and Torres Strait Islander children of Far North Queensland: a retrospective cohort study. Aust N Z J Public Health. 2019;43(4):319-27. https://doi.org/10.1111/1753-6405.12911



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Chapter 4 Anaemia in Early Childhood Among Aboriginal and Torres Strait Islander Children of Far North Queensland: A Retrospective Cohort Study

Table 4.1
List of Tables in article Anaemia in Early Childhood Among Aboriginal and Torres Strait Islander Children of Far North Queensland: A Retrospective Cohort Study.

Table 4.2
List of Figures in article Anaemia in Early Childhood Among Aboriginal and Torres Strait Islander Children of Far North Queensland: A Retrospective Cohort Study.

4.1 Article: Anaemia in Early Childhood Among Aboriginal and Torres Strait Islander Children of Far North Queensland: A Retrospective Cohort Study

Anaemia in early childhood among Aboriginal and Torres Strait Islander children of Far North Queensland: a retrospective cohort study

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Abstract

Objective: Early childhood anaemia affects health and neurodevelopment. This study describes anaemia among Aboriginal and Torres Strait Islander children of Far North Queensland.

Methods: This retrospective cohort study used health information for children born between 2006 and 2010 and their mothers. We describe the incidence of early childhood anaemia and compare characteristics of children and mothers where the child had anaemia with characteristics of children and mothers where the child did not have anaemia using bivariate and multivariable analysis, by complete case (CC) and with multiple imputed (MI) data.

Results: Among these (n=708) Aboriginal and Torres Strait Islander children of Far North Queensland, 61.3% (95%CI 57.7%, 64.9%) became anaemic between the ages of six and 23 months. Multivariable analysis showed a lower incidence of anaemia among girls (CC/MI p<0.001) and among children of Torres Strait Islander mothers or both Aboriginal and Torres Strait Islander mothers (CC/MI p<0.001) compared to children of Aboriginal mothers. A higher incidence of anaemia was seen among children of mothers with parity three or more (CC/MI p<0.001); children born by caesarean section (CC/MI p<0.001); and children with rapid early growth (CC/MI p<0.001).

Conclusion: Early childhood anaemia is common among Aboriginal and Torres Strait Islander children of Far North Queensland. Poor nutrition, particularly iron deficiency, and frequent infections are likely causes.

Implications for public health: Prevention of early childhood anaemia in 'Close the Gap' initiatives would benefit the Aboriginal and Torres Strait Islander children of Far North Queensland – and elsewhere in northern Australia.

Key words: anaemia, Aboriginal, Torres, child, mother, Queensland

Anaemia is a global health issue that particularly affects women and young children.[1] Causes of anaemia include nutrient deficiencies – lack of folate, vitamin B12 and/or iron-infections, inflammation and genetic conditions.[1]

Anaemia in the first thousand days, from conception to age two years, can compromise the health of mothers and their pregnancy outcomes as well as the health and early childhood development of their children.[2] The most common cause of anaemia in early life is iron deficiency, as iron requirements increase due to expanding blood supply and other tissue growth.[1,3] Prevention of iron deficiency and/or anaemia is necessary for optimal child health and development.[2,4]

During the first months of life, the main source of iron is not breast milk or infant formula but the iron provided to the baby by its mother during the last ten weeks of pregnancy.[5] Iron status of an infant at birth reflects the iron status of the mother during pregnancy.[6] In low-income settings, anaemia of a mother in pregnancy is a strong predictor of anaemia in the early life of her child.[7] Birthweight matters, as smaller babies have smaller iron endowment.[6] Cord clamping practices at birth are also important, as delayed clamping can increase body iron of the newborn by about 30% compared to early clamping.[8,9]

A baby of healthy birthweight, born at full term to a well-nourished mother, typically has sufficient iron for the first six months of life.[6,8] After this, nutrient-dense solid foods rich in iron are required.[10,11] Traditionally, Aboriginal and Torres Strait Islander Australians consumed many iron-rich foods such as insects, shellfish, animal blood and organs.[12-14] Today, however, Aboriginal and Torres Strait Islander people consume diets that are less nutritious than the diets of other Australians.[15] These nutrient-poor diets, often commencing from early life, are associated with high rates of food insecurity compared to other Australians, especially among those living in remote locations.[15-17] Food insecurity increases the risk of anaemia among women and their children.[18]

Anaemia among Aboriginal and Torres Strait Islander children is a long-standing concern in remote communities in the Northern Territory and Western Australia.[19-22] A recent Northern Territory report showed 29.0% of children

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aged six to 23 months (n=956) were anaemic in 2016/17.[23]

Comparable information on anaemia among other Australian children is limited. Localised surveys (2010) reported 1–6% of toddlers had iron deficiency anaemia increasing to 14% among those of Asian background, while one national survey from 1995 reported that 2% of 1–4-year-old children were anaemic.[24-26]

In remote Far North Queensland (Map 1), 71.5% of the population are Aboriginal and/or Torres Strait Islander people (n=14,107).[27] A recent audit from eight Cape York Aboriginal communities reported that 32.3% of children aged six to 23 months were anaemic.[28] However, published information is lacking for the wider Far North Queensland region.

The current study was undertaken to investigate anaemia among Aboriginal and Torres Strait Islander mothers and their children in Far North Queensland. Here we describe early childhood anaemia, defined as anaemia at age six to 23 months, and the characteristics associated with early childhood anaemia among Aboriginal and Torres Strait Islander children.

Methods

This retrospective cohort study used information from three existing health service data collections, extracted, linked and de-identified by the Queensland Health Statistical Services Branch. The process of securing this information has been previously described.[29] Briefly, data recorded between 2000 and 2015 were extracted from the Queensland Perinatal Data Collection (PDC)[30]; the Queensland Health Pathology Services Data Collection (Auslab)[31]; and the community health services electronic record system, Ferret,[32] used mainly in remote Far North Queensland (Map 1 and Supplementary Table 1).

Study data were provided for two cohorts of Aboriginal and Torres Strait Islander children and their mothers: the Cape York cohort and the 2009–2010 cohort. The Cape York cohort includes children of the remote Cape York communities only, born between 2006 and 2008. The 2009–2010 cohort includes children born to Aboriginal and/or Torres Strait Islander mothers with a Queensland Perinatal Data Collection (PDC) record of birth in 2009 or 2010 in Far North Queensland, which includes the Torres region, Cape York and Cairns and Hinterland. Children included in this analysis are those with a Ferret record in addition to a PDC record. The Ferret system was implemented mainly in discrete Aboriginal and Torres Strait Islander communities across Far North Queensland (Map 1). Twelve of these localities were in Cape York, 21 in the Torres region and five in the Cairns and Hinterland region.

Longitudinal information on child growth and haemoglobin levels was recorded on the Ferret system. To ensure independence of events for statistical analysis, only the first child born to each mother between 2006 and 2010 was included.

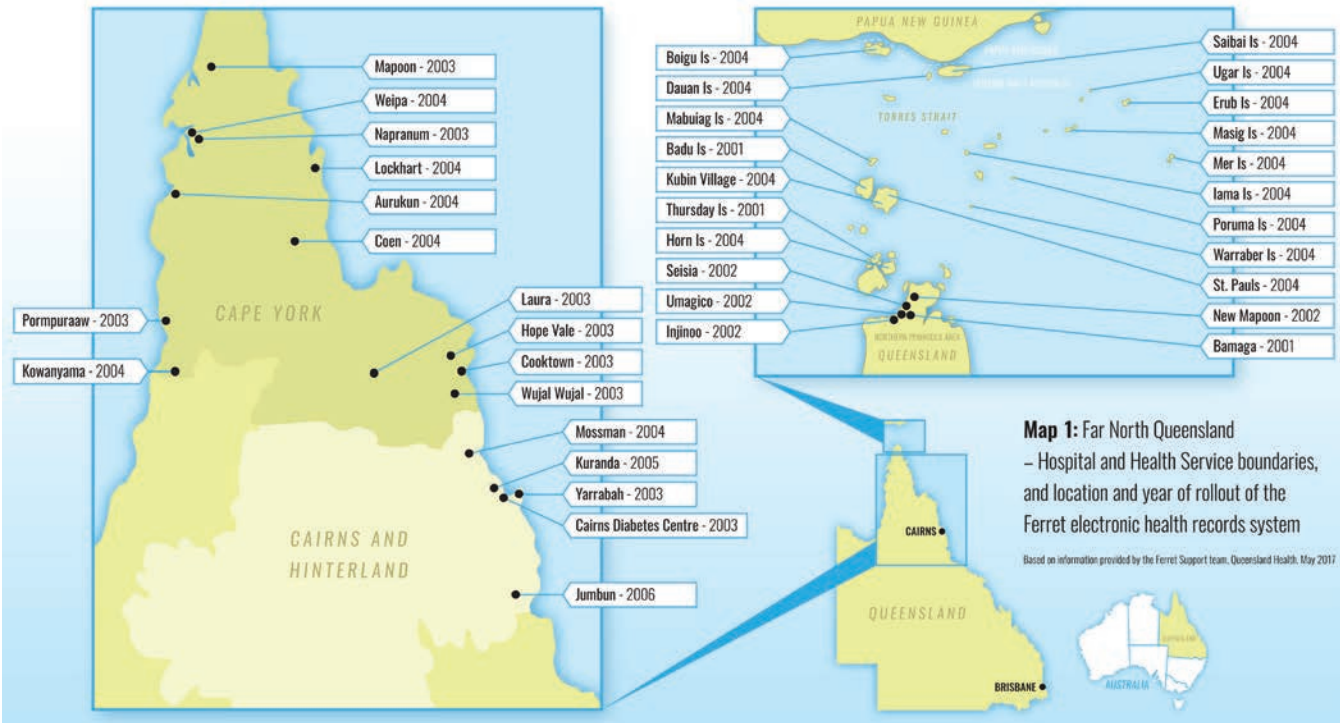
Ethics approval was granted by Queensland Health Far North Queensland Human Research Ethics Committee (HREC/15/QCH/50-980) in June 2015. Approval under the Queensland Public Health Act 2005 was granted by the Director-General of Queensland Health in February 2016. The complete linked de-identified data was provided to the research group in May 2017.

Study variables and definitions

Anaemia was defined as per Queensland Health clinical guidelines (haemoglobin <105 g/L from six to 11 months; haemoglobin <110g/L for children from 12 to 23 months).[33] Children aged six to 23 months, with at least one haemoglobin level recorded below the respective criteria for age at the date of measurement, were considered to have anaemia. The haemoglobin levels reported here for children were measured on capillary blood using a HemoCue®.

Some characteristics are as reported on the Perinatal Data Collection[30] (mother's usual residence, ethnicity, parity, smoking in pregnancy, pregnancy induced

Map 1: Caption Far North Queensland – Hospital and Health Service boundaries and localities of Ferret electronic health records system.



hypertension; baby's sex, gestational age at birth, birthweight, method of birth). Birthweight z-scores adjusted for sex and gestational age, for babies with gestational age of 33 weeks or more were calculated using the INTERGROWTH-21ST Neonatal Size Calculator.[34,35] The INTERGROWTH-21st standards for newborns are designed to complement the WHO Child Growth Standards.[34] Weight for age z-scores for the first weight measure at age four to six months recorded on the Ferret system were calculated using the STATA 'zscore06' module, which is based on the 2006 World Health Organization sex-specific child growth standards.[36,37]

Where measurements were available, z-score-change was calculated (z-score for the first weight measurement at age four to six months minus birthweight z-score for weight for gestational age). Z-score-change is a measure of change in weight for age z-scores in the first months of life. A positive value indicates an increase in weight for age, a negative value indicates a decline in weight for age, while a zero value indicates no change in weight for age (Supplementary Table 2).

Other characteristics (maternal body mass index [BMI] and age; baby's prematurity and/or low birthweight) were derived from Perinatal Data Collection information using criteria specified by the Australian Institute of Health and Welfare and the National Health and Medical Research Council, unless otherwise referenced.[38,39] Information on maternal glucose tolerance, haemoglobin, ferritin, red cell folate (RCF) and vitamin B12 levels are as recorded on the Queensland Pathology Auslab system. Maternal anaemia in the third trimester of pregnancy was defined as an Auslab record of mother's haemoglobin level <110 g/L as per Queensland Health clinical guidelines, measured on a date between estimated day 186 of pregnancy and the date of birth of the child.[24,40] Supplementary Table 2 provides further details on definitions including implausibility criteria. Implausible values were considered missing.

The Socio-Economic Index for Areas (SEIFA 2011) ranks Australian Bureau of Statistics Statistical Local Areas (SLA) by deciles of relative socio-economic advantage and disadvantage.[41] A ranking of '1' indicates greatest relative disadvantage while a ranking of '10' indicates greatest relative advantage. The appropriate SEIFA decile ranking was allocated to each mother based on her usual place of residence.

Statistical analysis

Categorical variables were described using absolute and relative frequencies. The distributions of numerical variables were assessed; symmetrically distributed numerical characteristics were described using mean values, 95% confidence intervals (95%CI), and ranges; numerical values with a skewed distribution were described using median, inter-quartile ranges (IQR) and ranges. The cumulative incidence of anaemia between age six to 23 months was presented with 95% confidence interval (95%CI). Mean haemoglobin levels using the first haemoglobin reading for each child, and incidence of anaemia were presented by six-month age groups (six–11 months, 12–17 months, 18–23 months). Children were included in one or more of the six-month age intervals if the appropriate measurements were available at that age but once only in analysis for the six to 23-month age group. Characteristics of the children and their mothers were compared between those children who had early childhood anaemia and those who did not, using bivariate logistic regression analyses adjusted for cohort.

The following characteristics were considered during multivariable analyses (Cohort 1 "2009-2010 cohort" n=407; Cohort 2 "Cape York cohort" n=301): sex of the baby; birthing method (non-instrumental vaginal, instrumental vaginal, caesarean section); gestational age of baby; whether baby was premature or not; birthweight of baby; z-score-change (z-score for weight for age at first weight at age four to six months less z-score for birthweight); feeding method to age four months (only breast milk, only infant formula, both breast milk and formula); ethnicity of mother (Aboriginal, Torres Strait Islander, both); region of residence of mother; SEIFA category for residence of mother; age of mother when baby was born; BMI category of mother (underweight, normal weight, overweight, obese); categories of parity (0-2, >=3); smoking during pregnancy; five or more antenatal care visits; pregnancy induced hypertension; mother had pre-existing diabetes; mother had gestational diabetes); low RCF level before or during pregnancy; low B12 level before or during pregnancy; mother anaemic in the third trimester of pregnancy.

Multivariable logistic regression analyses were conducted to identify independent risk factors for early childhood anaemia for the complete case analysis. Backward and forward stepwise modelling procedures were initially conducted to establish basic multivariable models for the combined cohorts. Characteristics that were not part of the basic models were assessed for potential confounding effects. A confounder was assumed to be a variable that changed estimates of characteristics in the basic model by 10% or more.[42]

Multivariable multiple imputation was conducted using Stata's MI commands for sequential imputation using chained equations. Missing values were imputed for BMI of mother; parity; smoking during pregnancy; mother anaemic in the third trimester of pregnancy; mother with pre-existing diabetes; mother with gestational diabetes; number of antenatal visits five or more; feeding method to age four months; and z-score-change from birth to age four to six months. Low RCF and B12 levels before or during pregnancy were not imputed because these characteristics were missing in close to 80% of cases. Examination of patterns of missing data was conducted using Pearson's chi-square and Fisher's exact tests to compare the occurrence of missing values in characteristics (Supplementary Table 3). Patterns of missing values were assessed and judged to be "missing at random".[43] Linear regression was used to impute missing values of continuous characteristics; logistic regression was used to impute missing values of dichotomous characteristics; ordinal logistic regression was used to impute missing values of the categories of BMI. Imputation models were based on the following variables with nil missing data: early childhood anaemia; sex of baby; gestational age of baby; baby premature; birthing method; birthweight of baby; pregnancy induced hypertension, ethnicity of mother, age of mother, SEIFA index; antenatal care received; and cohort. Forty imputed data sets were created. Multivariable logistic regression analyses were conducted to identify independent risk factors for early childhood anaemia for imputed data.

Results of multivariable models for complete case and imputed data analyses are presented as odds ratios (OR) and 95% confidence intervals. P values of less than 0.05 were considered statistically significant.

Figure 1: Flow diagram – early childhood anaemia among two cohorts of Aboriginal and Torres Strait Islander children and their mothers in Far North Queensland; data available and exclusions.

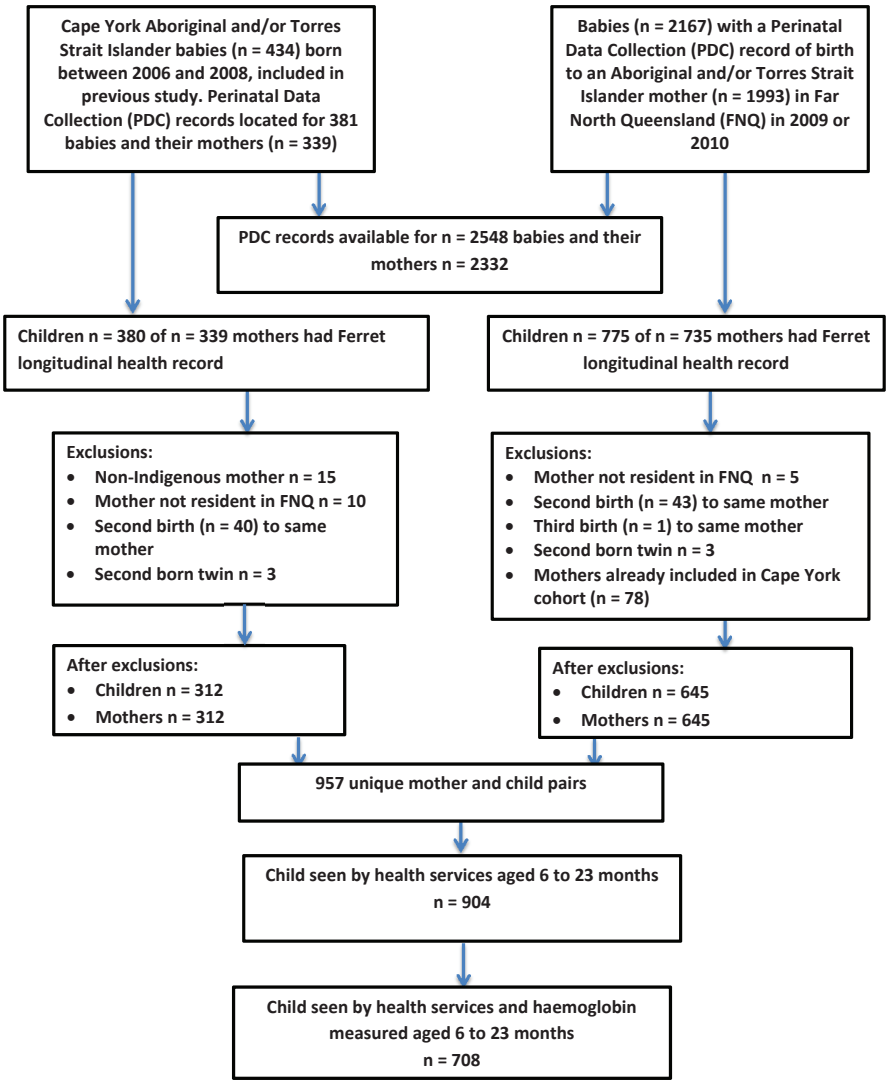
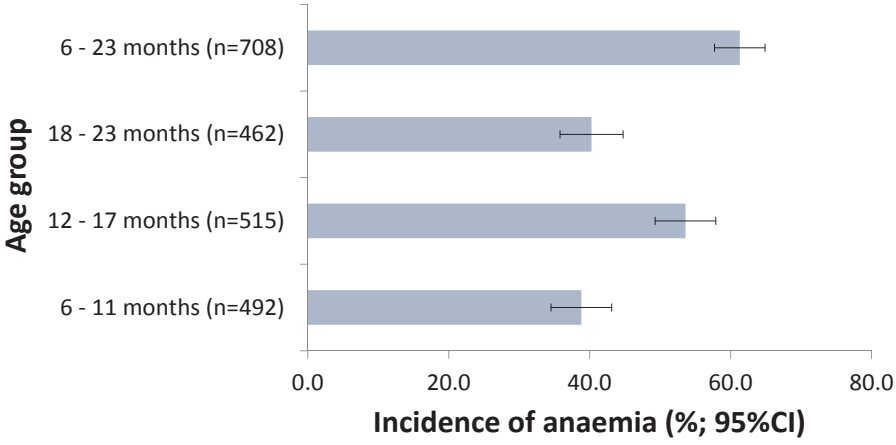


Figure 2: Incidence of anaemia among Aboriginal and Torres Strait Islander children (n = 708) of Far North Queensland from age six to 23 months, and by six-month age groups (%, 95% confidence interval).



Analysis was conducted using Stata version 13 (StataCorp, Lakeway Drive, College Station, Texas).

Results

Linked de-identified data was provided in May 2017 for 2,548 Aboriginal and Torres Strait Islander children born to 2,332 mothers in Far North Queensland between 2006 and 2010. Ferret records were available for 1,155 children of 1,074 mothers. The number of children for whom this information was available is close to the estimated 1,147 child residents based on census population figures for those localities (Figure 1, Map 1, Supplementary Table 4). Information was excluded where the mother was non-Indigenous (n=15), not resident in Far North Queensland (n=15) and where the child was not the first child born to his/her mother in the cohort years (n=90). Seventy-eight mothers were excluded from the 2009–2010 cohort because they were already included in the Cape York cohort. After exclusions, the number of unique mother and child pairs was 957 (Figure 1).

Ferret records showed at least one visit to health services between age six and 23 months for 904 (94.5%) of these 957 children, of whom 708 (74.0%) had a haemoglobin level recorded at least once between the ages of six and 23 months (Supplementary Tables 5 and 6). No significant differences were seen between children for whom haemoglobin measurements were available and those without haemoglobin measurements, except that children from Cape York were more likely to have been seen by health services and have had a measurement of haemoglobin made, compared to children from elsewhere ($p<0.001$), see Supplementary Tables 5 and 6.

Of these 708 children, 61.3% (95%CI 57.7%, 64.9%) had at least one haemoglobin measure showing anaemia; the incidence of anaemia by six-month age groups was highest at 12–17 months (Figure 2). Mean haemoglobin was above the level indicating anaemia (105 g/L) at six to 11 months; 109.8 g/L (95%CI 108.7,110.9) but below the level indicating anaemia (110 g/L) at 12–17 months; 109.3 g/L 95%CI 108.3, 110.3) and close to that level (110 g/L) at 18–23 months; 111.8 (95%CI 110.8, 112.8), see Supplementary Figure 1. Among children anaemic at six to 11 months who had subsequent haemoglobin measurements, 102 out of 150 (68%) were also anaemic at

12–17 months and 69 out of 138 (50%) at 18–23 months.

Haemoglobin measurements were not available for 249 children between the age of six and 23 months. If it is assumed that all these children did not have anaemia, the number of children without anaemia (n=249 + 274) would be n=523. Under this hypothetical assumption, the incidence of early childhood anaemia would be 45.4% (95%CI 42.2%, 48.5%).

Bivariate analysis (n=708) showed the incidence of early childhood anaemia was higher among boys (65.8%) compared to girls (56.5%, $p<0.001$) and among children born by caesarean section (69.5%) compared to those born by vaginal birth (57.7%, $p<0.001$). Children who had early childhood anaemia had lower mean birthweight (3,159g vs. 3,217g, $p=0.01$) and lower mean birthweight z-score (+0.082 vs. +0.274, $p=0.001$), and higher mean gains in z-score (+0.254 v-0.013, $p<0.001$) for weight for age in early life, see Tables 1a and 1b).

Children of Aboriginal mothers (71.4%) had higher incidence of early childhood anaemia than children of mothers who were Torres Strait Islander (46.9%) or both Aboriginal and Torres Strait Islander (43.9%, $p<0.001$), see Table 2).

Multi-variable analysis (Table 3) showed higher incidence of early childhood anaemia among children born by caesarean section compared to children born by vaginal birth ($p<0.001$), children with higher gains in weight for age ($p<0.001$) and children of mothers with a parity of three children or more ($p<0.001$), and lower incidence of early childhood anaemia among girls compared to boys ($p<0.001$). Children whose mothers were Torres Strait Islander ($p<0.001$) or both Aboriginal and Torres Strait Islander ($p<0.001$) had lower incidence of early childhood anaemia compared to children whose mothers were Aboriginal (Table 3). The analysis was repeated using mother's region of residence instead of mother's ethnicity. Children of mothers who were resident in the Torres Strait and Northern Peninsula Area (MI $p=0.003$) and children of mothers resident in Cairns and Hinterland (MI $p=0.005$) had lower incidence of early childhood anaemia compared to children of mothers resident in Cape York (Supplementary Table 7).

Multi-variable analysis showed disparate results in respect of smoking in pregnancy. Multiple imputation analysis, but not complete case analysis, showed significantly higher incidence of early childhood anaemia among children of mothers who smoked in pregnancy compared to children of mothers who did not smoke in pregnancy (MI $p=0.023$), see Table 3. Birthweight, age of mothers and anaemia of mothers in the third trimester of pregnancy were found to be confounding factors in multivariable analyses.

Discussion

This study shows that early childhood anaemia was common among these (n=708) Aboriginal and Torres Strait Islander children of Far North Queensland with the incidence of anaemia being 61.3% between the age of six and 23 months. Many children with anaemia before the age of 12 months were still anaemic in the second year of life. Mean haemoglobin levels were low; below the diagnostic level for anaemia from 12 to 17 months. Our findings are consistent with reports of high rates of early childhood anaemia among Aboriginal and Torres Strait Islander infants and young children elsewhere in northern Australia.[24,44,45]

Table 1a: Incidence of Early Childhood Anaemia (anaemia between age six and 23 months) among Aboriginal and Torres Strait Islander children (n=708) of Far North Queensland by characteristics of the children.

Characteristics of children	n	Child ever anaemic age 6–23 months n (%) [95%CI]	P value (logistic regression adjusted for cohort – unless stated otherwise)
Cohorts:			
Both combined	708	434 (61.3%) [57.7%, 64.9%]	n/a
2009–2010 births cohort	407	199 (48.9%) [44.1%, 53.8%]	chi2 <0.001
Cape York cohort	301	235 (78.1%) [73.4%, 82.8%]	
Gender:			
Male	363	239 (65.8%) [60.9%, 70.7%)	<0.001
Female	345	195 (56.5%) [51.3%, 61.8%]	
Birth method:			
Vaginal	473	273 (57.7%) [53.2%, 62.2%]	base
Vaginal/Instrumental	35	22 (62.9%) [46.0%, 79.7%]	<0.001
Caesarean	200	139 (69.5%) [63.1%, 75.9%]	<0.001
Birth Weight category:			
Low birth weight (<2,500g)	81	52 (64.2%) [53.5%, 74.9%]	0.008
Normal (2,500–4,000g)	580	355 (61.2%) [57.2%, 65.2%]	base
Marcosomic (>=4,000g)	47	27 (57.4%) [42.8%, 72.1%]	0.782
Gestational age category:			
Preterm (<37 weeks)	82	50 (61.0%) [50.2%. 71.8%]	0.893
Full-term (>=37 weeks)	626	384 (61.3%) [57.5%, 65.2%]	
Feeding method birth to 4-6 months; n=544 (164 missing)			
Only breast milk	228	157 (68.9%) [62.8%, 74.9%]	base
Only infant formula	56	30 (53.6%) [40.1%, 67.0%]	0.249
Breast milk and formula	260	159 (61.2%) [55.2%, 67.1%]	0.018

Table 1b: Incidence of Early Childhood Anaemia (anaemia between age six and 23 months) among Aboriginal and Torres Strait Islander children (n = 708) of Far North Queensland by characteristics of the children.

Characteristics of children	All n=708	Ever anaemic age 6–23 months n=434	Not anaemic age 6–23 months n=274	P value (logistic regression adjusted for cohort)
Gestational age at birth weeks – median (IQR) [range]	39 (38–40) [26–42]	39 (38–40) [27–42]	39 (38–40) [26–42]	0.036
Birth weight - grams mean (95% CI) [range]	3,181 (3,136, 3,225) [800–5,320]	3,159 (3,102, 3,215) [800–5,320]	3,217 (3,145, 3,288) [960–4,780]	0.010
Z-score for birth-weight for gestational age mean (95%CI) [range] n=692 (missing n=16)	+0.16 (+0.07, +0.24) [-2.9–+4.3] n=692	+0.082 (-0.021, +0.18) [-2.9–+4.3] n=426	+0.274 (+0.142, +0.405) [-2.4–+3.2] n=266	0.001
Z-score-change birth to first weight at age 4 -6 months mean (95% CI) [range] n=527(missing n=181)	0.16 (+0.057, +0.255) [-3.7–+3.7] n=527	+0.254 (+0.125, +0.382) [-3.7–+3.7] n=334	-0.013 (-0.167, +0.140) [-3.5–+3.0] n=193	<0.001

The finding of more early childhood anaemia among children born by caesarean or vaginal/instrumental births may reflect the urgency of such births, with early cord clamping reducing transfer of placental blood to the newborn.[8,9] Caesarean births are increasing among Indigenous mothers; this finding may be particularly relevant for the Torres Strait where diabetes in pregnancy and births by caesarean section are common.[46,47]

Table 2: Incidence of Early Childhood Anaemia (anaemia between age six and 23 months) among Aboriginal and Torres Strait Islander children (n = 708) of remote Far North Queensland by characteristics of their mothers

Characteristics of mothers	n	Child ever anaemic age 6–23 months n (%) [95%CI]	P value (logistic regression adjusted for cohort)
Ethnicity			
Aboriginal	423	302 (71.4%) [67.1%, 75.7%]	base
Torres Strait Islander	228	107 (46.9%) [40.4%, 53.5%]	<0.001
Both Aboriginal and Torres Strait Islander	57	25 (43.9%) [30.6%, 57.1%]	<0.001
Region of residence			
Cairns and Hinterland	56	29 (51.8%) [38.3%, 65.3%]	0.025
Cape York	442	318 (72.0%) [67.7%, 76.2%]	base
Torres Strait and Northern Peninsula Area	210	87 (41.4%) [34.7%, 48.1%]	0.023
SEIFA – usual residence			
Mother resident in SEIFA 1	620	377 (60.8%) [57.0%, 64.7%]	0.509
Mother resident in SEIFA 2 - 10	88	57 (64.8%) [54.6%, 75.0%]	
Body Mass Index of mothers (n=481, missing n=227)			
Underweight (9.8%)	47	34 (72.3%)[59.1%, 85.6%]	0.037
Healthy weight (35.8%)	172	93 (54.1%) [46.5%, 61.6%]	base
Overweight (25.2%)	121	63 (52.1%) [43.0%, 61.1%]	0.459
Obese (29.3%)	141	68 (48.2%) [39.9%, 56.6%]	0.032
Teenage mothers			
Teenage mother	163	95 (58.3%) [50.6%, 65.9%]	0.162
Mother age 20 years or older	545	339 (62.2%) [58.1%, 66.3%]	
Antenatal visits (missing n=1)			
Less than 5 visits	83	43 (51.8%) [40.8%,62.8%]	<0.001
5 visits or more	642	390 (62.5%) [58.7%, 66.3%]	
Parity (missing n=233)			
nil to 2	277	161 (58.1%) [52.3%, 64.0%]	0.103
3 or more	198	127 (64.1%) [57.4%, 70.9%]	
Smoked in pregnancy (n=703, missing n=5)			
Yes	439	275 (62.6%) [58.1%, 67.2%]	0.020
No	264	155 (58.7%) [52.7%, 64.7%]	
Gestational Diabetes (n=421, missing n=287)			
Yes	75	42 (56.0%) [44.5%, 67.5%]	0.329
No	346	198 (57.2%) [52.0%, 62.5%]	
Pre-existing Diabetes (n=587, missing n=121)			
Yes	33	23 (69.7%) [53.1%, 86.2%]	<0.001
No	554	330 (59.6%) [55.5%, 63.7%]	
Pregnancy Induced Hypertension (PIH)			
Yes	45	31 (68.9%) [54.8%, 83.0%]	0.026
No	663	403 (60.8%) [57.1%, 64.5%]	
Anaemia in third trimester (n=657, missing n=51)			
Yes	336	202 (60.1%) [54.9%, 65.4%]	0.014
No	321	199 (62.0%) [56.7%, 67.3%]	
Iron deficiency in pregnancy (n=385, missing n=323)			
Yes	185	110 (59.5%) [52.3%, 66.6%]	0.775
No	200	123 (61.5%) [54.7%, 68.3%]	
Low Red Cell Folate (RCF) before/during pregnancy (n=158, missing n=550)			
Yes	20	16 (80.0%) [60.8%, 99.2%]	<0.001
No	138	71 (51.5%) [43.0%, 59.9%]	
Low B12 before/during pregnancy (n=131, missing n=577)			
Yes	22	7 (31.8%) [10.7%, 53.0%]	0.151
No	109	62 (56.9%) [47.4%, 66.3%]	

Our findings show that children of Aboriginal mothers had higher incidence of early childhood anaemia compared to children of mothers who were Torres Strait Islander or both Aboriginal and Torres Strait Islander. Further analysis by mother's region of residence showed the same pattern. These results reflect the different history of Aboriginal people of Cape York compared to people of the Torres Strait. Government policies forcibly relocated Queensland Aboriginal people from their traditional lands to mission settlements, some of which are now the remote communities of Cape York.[48] This "large scale relocation did not occur in the Torres Strait".[48] Despite Government restrictions and impositions, Torres Strait Islander peoples largely remained on their traditional lands, a key factor in preserving cultural continuity, including traditional food systems.[48]

The high cost of nutritious food has been widely reported, while household food insecurity is exacerbated by smoking.[49,50] The implications of poor health of mothers on the future health of their children have been raised previously.[51] The intergenerational association reported here, of high parity and maternal smoking with early childhood anaemia, reflects the shared experiences of food insecurity of these mothers and their children in a context of poverty and social disadvantage that is particularly challenging in Cape York.[48]

The limitations of this study are those associated with the use of routine health service data, including missing information.[29] The multiple imputation methodology was used to adjust for missing values and results are presented for both complete case and multiple imputation analyses. However, some information was not recorded on the electronic data collections accessed for this study. For example, information about treatment of anaemia was not available for mothers or children. It may be that treatment of maternal anaemia protects the unborn child from subsequent anaemia, but this hypothesis could not be tested. Similarly, the lack of information on treatment of children meant that the effect of treatment at first diagnosis of early childhood anaemia on subsequent haemoglobin levels could not be assessed.

In addition, many (26.0%) of the 957 children with a Ferret record did not have a measure of haemoglobin recorded between the age of six and 23 months; most (n=196, 20.5%) were

Table 3: Risk factors for Early Childhood Anaemia (n=708); multi-variable analysis – complete case analysis and analysis with imputed data.

	Complete case analysis n=329					Imputed data analysis n=708			
Characteristic	**Anaemia n=203 (61.7%)**	**No Anaemia n=126 (38.3%)**	**Odds-ratio (95% CI)[a]**	***p*-value**	**Number of missing values (%)**	**Anaemia n=434 (61.3%)**	**No Anaemia n=274 (38.7%)**	**Odds-ratio (95% CI)[a]**	***p*-value**
Sex of child					0				
Male	115 (56.7%)	59 (46.8%)	1			239 (55.1%)	124 (45.3%)	1	
Female	88 (43.4%)	67 (53.2%)	0.63 (0.59, 0.67)	P<0.001		195 (44.9%)	150 (54.7%)	0.62 (0.55, 0.71)	P<0.001
Z-score-change from birth to 4 to 6 months	/	/	1.3 (1.2, 1.4)	p<0.001	181 (25.6%)	/	/	1.2 (1.1, 1.3)	P<0.001
Age of mother[b]	/	/	0.97 (0.92, 1.02)	P=0.224	0	/	/	0.99 (0.98, 1.00)	P=0.096
Ethnicity of mother					0				
Aboriginal	144 (70.9%)	55 (43.7%)	1			302 (69.6%)	121 (44.2%)	1	
Torres Strait Islander	46 (22.7%)	54 (42.9%)	0.34 (0.21, 0.53)	P<0.001		107 (24.7%)	121 (44.2%)	0.35 (0.22, 0.56)	P<0.001
Both	13 (6.4%)	17 (13.5%)	0.26 (0.17, 0.39)	P<0.001		25 (5.8%)	32 (11.7%)	0.28 (0.19, 0.42)	P<0.001
Parity					233 (32.9%)				
Up to 2 children	124 (61.1%)	79 (62.7%)	1			284 (65.4%)	193 (70.4%)	1	
3 or more children	79 (38.9%)	47 (37.3%)	2.1 (1.7, 2.5)	P<0.001		150 (34.6%)	81 (29.6%)	1.8 (1.4, 2.5)	P<0.001
Birth method					0				
Vaginal	125 (61.6%)	100 (79.4%)	1			273 (62.9%)	200 (73.0%)	1	
Vaginal instrumental	8 (3.9%)	3 (2.4%)	3.1 (1.9, 5.2)	P<0.001		22 (5.1%)	13 (4.7%)	1.4 (1.1, 1.9)	P=0.013
Caesarian	70 (34.5%)	23 (18.3%)	3.0 (2.9, 3.1)	P<0.001		139 (32.0%)	61 (22.3%)	1.7 (1.4, 2.1)	P<0.001
Mother anaemic in third trimester[b]					51 (7.2%)				
No	103 (50.7%)	63 (50.0%)	1			216 (49.8%)	131 (47.8%)	1	
Yes	100 (49.3%)	63 (50.0%)	1.0 (0.5, 2.2)	P=0.934		218 (50.2%)	143 (52.2%)	0.89 (0.77, 1.03)	P=0.122
Mother smoked during pregnancy					5 (0.7%)				
No	75 (37.0%)	50 (39.7%)	1			156 (35.9%)	109 (39.8%)	1	
Yes	128 (63.1%)	76 (60.3%)	1.0 (0.7, 1.5)	P=0.964		278 (64.1%)	165 (60.2%)	1.2 (1.02, 1.3)	P=0.023

Notes:

Both models were adjusted for the confounding effect of birth weight (no missing values imputed).

a: 95% CI = 95% confidence interval.

b: Mother anaemic in third trimester and mothers' age were identified as confounding variables in complete case data analysis. Imputed data are averages of 40 imputations.

seen by health services but haemoglobin levels were not recorded. Children in Cape York were more likely to be seen and to have a haemoglobin level recorded than children from elsewhere. No other differences were identified. However, the reason for this missing data is not known and there may be an unidentified bias in the availability of relevant information.

Another limitation of our study is that haemoglobin levels were measured on capillary blood using HemoCues®. The use of capillary blood and these devices may underestimate haemoglobin levels, which would result in overestimation of the incidence and prevalence of anaemia.[52] Validation studies suggest that the HemoCue® is suitable for screening purposes but, where anaemia is suspected, other methods should also be used.[53] However, health service protocols for diagnosis and treatment of anaemia in remote Far North Queensland are based on HemoCue® measurements.[33]

The information presented here is for children born between 2006 and 2010. It is possible that the situation in respect of early childhood anaemia has changed. However, in Cape York in 2014 and 2015, about one-in-three children aged six to 23 months were anaemic (n=155, 32.3% anaemic, 95%CI 24.8%, 39.7%) indicating that early childhood anaemia continues to be a problem in Cape York.[28] Comparable information is not available from elsewhere in Far North Queensland.

There is no information to identify the cause(s) of the anaemia reported here. Nutrient deficiencies such as iron deficiency cause anaemia, as do chronic infections.[1,54] Iron deficiency is the 'usual suspect' as a nutrition-related cause of anaemia in early life because of the high requirements for iron due to rapid growth.[10] Iron requirements per kilogram of body weight are higher at six to 12 months than at other stages of the life cycle.[5] Australian estimates show that the daily iron requirements of a child aged seven to 12 months are higher than those of an adult man: Estimated Average Requirement (EAR) child seven to 12 months – 7mg; EAR male aged 19 years or more – 6mg.[55] Milk is not a rich source of iron; during the first months of exclusive breastfeeding, a baby draws on iron stores acquired before birth from the mother.[5] Subsequently the small quantity of solid food consumed by young children must provide most of these high iron requirements.[10] Consequently, iron-rich and/or iron-fortified first foods are recommended in Australia.[11]

Two studies in the Northern Territory showed the association of iron deficiency with childhood anaemia in similar settings. In one study, among young Aboriginal children (n=74) with anaemia, most (n=62, 84%) had iron deficiency anaemia, with folate deficiency and chronic infections identified as causes of anaemia in the other children.[21] Another Northern Territory study among school-age children with anaemia (n=201) found that iron therapy was effective in resolving anaemia among 83% of the 66 children for whom follow-up measurements were available.[22]

Several of the risk factors identified here are consistent with iron deficiency as a cause of the anaemia: birth by caesarean section; rapid early growth; and boys compared to girls, as boys typically have higher early weight gains than girls.[56,5]

Infections are another probable cause of anaemia in these children, with high rates of infectious diseases reported for Aboriginal and Torres Strait Islander children of remote Far North Queensland.[57] There is a bidirectional relationship between infectious disease and nutrition status; frequent illness impairs nutrition status and poor nutrition status increases susceptibility to infection.[58] The immune response to infections restricts iron availability to infectious organisms; when prolonged, this immune response can lead to anaemia.[59]

However, the diagnosis of anaemia based on haemoglobin only, as in this study, cannot identify the cause(s) of anaemia. The lack of information on the causes of early childhood anaemia is not only a limitation of this study but also a limitation of methods currently available to identify causes of anaemia in early childhood; in particular, the assessment of iron status is complex in the presence of infection.[60,54]

Prevention of early childhood anaemia is important as successful treatment of anaemia may not reverse the associated neurological deficits.[2] Where the prevalence of early childhood anaemia is high (20% or more), WHO recommends interventions that combine promotion of breastfeeding and healthy food with home fortification of solid foods using multi-micronutrient preparations for babies/children aged six to 23 months.[1,61-63] Such interventions have been demonstrated to be acceptable, safe and effective in the prevention and treatment of early childhood anaemia in low-income settings where the infectious disease burden is high.[61-63] One such intervention, the Fred Hollows Foundation Early Childhood Nutrition and Anaemia Prevention Project (ECNAPP), was successfully piloted in six remote communities across northern Australia in 2010–2012.[64] Nutrition-focused interventions will be strengthened by complementary interventions to improve food security and reduce infections in early life.[58]

Improved nutrition in the first one thousand days of life – through pregnancy up to the age of two years – provides "a golden opportunity to impact neurodevelopment and brain function through the lifespan".[2] Prevention of early childhood anaemia, included as a key strategy to 'Close the Gap' between Aboriginal and Torres Strait Islander Australians and other Australians,[65] would benefit the Aboriginal and Torres Strait Islander children of Far North Queensland – and elsewhere in northern Australia.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary Figure 1: Mean haemoglobin (g/L) (with 95% confidence interval) for Aboriginal and Torres Strait islander children of Far North Queensland by six month age groups.

Supplementary Table 1: Data collections used to source information to investigate Early Childhood Anaemia (anaemia at age six to 23 months) among Aboriginal and Torres Strait Islander children in Far North Queensland.

Supplementary Table 2: Definitions of variables used to describe characteristics of Aboriginal and Torres Strait Islander children (born between 2006 and 2010) and their mothers in Far North Queensland.

Supplementary Table 3: "Missingness" of characteristics in analysis of risk factors for early childhood anaemia in 708 Aboriginal children from North Queensland.

Supplementary Table 4: Early childhood anaemia among two cohorts of Aboriginal and Torres Strait Islander children and their mothers in Far North Queensland; comparisons of study participant numbers with census information.

Supplementary Table 5: Far North Queensland Aboriginal and/or Torres Strait Islander children with a Ferret record (n = 957): comparing those seen by health services at age six to 23 months (n = 904) with those not seen (n = 53).

Supplementary Table 6: Far North Queensland Aboriginal and/or Torres Strait Islander children with a Ferret record seen by health services at age six to 23 months (n = 904) - comparing those with at least one haemoglobin measure (n = 708) with those with no haemoglobin measure (n = 196) at age six to 23 months.

Supplementary Table 7: Risk factors for Early Childhood Anaemia (anaemia between six and 23 months) among Aboriginal and Torres Strait Islander children of Far North Queensland (n = 708): Results of multi variable analysis using region of residence of mother instead of ethnicity in imputed data model (all other variables as in Table 3).

4.2 Supplementary Materials

Supplementary Table 4.1
Data Collections - Information sources accessed to investigate the relationship between early childhood anaemia and developmental indicators at school entry age.

Year Commenced	Data Collection
1986	**Queensland Perinatal Data Collection (PDC)**
	Information on Queensland mothers and their babies is recorded at the time of birth on the Perinatal Data Collection, which commenced in Queensland in 1986. Information is collected on all live births in Queensland and on all stillbirths of at least 20 weeks gestation and/or at least 400g in weight.[1]
2001	**Ferret**
	A centralised electronic patient information and recall system rolled out in health services in Far North Queensland from 2001 to 2006.2 3 Ferret was used mainly by community health services in thirty three remote Aboriginal and Torres Strait Islander communities (Torres Strait (n = 21) and Cape York (n = 12)) plus five locations in the vicinity of Cairns. The Ferret system rollout was completed in 2006. [2,3] Data recorded on Ferret includes information from routine adult health checks, antenatal and child health checks. Ferret was the only system in use for this purpose during the timeframe of this research
1999	**Auslab**
	Pathology Queensland provides pathology services to all Queensland Health facilities. Pathology test results are recorded on centralised electronic systems. The Auslab system, which commenced in 1999, was in use for this purpose during the timeframe of this research. [4]

Year Commenced	Data Collection
2009	**The Australian Early Development Census (AEDC) Data Collection** Every three years, the Australian Department of Education the conducts the Australian Early Development Census. Every child commencing full time school in that year in Australia is assessed by his/her teacher for early childhood development in respect of: • Physical health and well-being • Social competence • Emotional maturity • Language and cognitive skills (school-based) • Communication and general knowledge

Footnotes

Each child is allocated a composite score and assigned to one of three categories: on track, at risk, or vulnerable [5, 6] Criteria for categories are based on the first AEDC conducted in 2009 and applied each year subsequently. Australian Early Development Censuses have been conducted on children enrolled in their first full time year of school, in 2009, 2012, 2015 and 2018

Supplementary Table 4.1 References

1. Queensland Health. Queensland Perinatal Data Collection Manual for the completion of Perinatal Data Queensland Health, 2016.
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Supplementary Table 4.2
Anaemia in early childhood. Definitions of variables used to describe characteristics of Aboriginal and Torres Strait Islander children (born between 2006 and 2010) and their mothers in Far North Queensland.

	Characteristics of Mothers
Maternal age	Age of a mother in completed years at the time of the birth of her baby.[1]
Teenage mother	Mother was aged less than twenty years at the birth of her baby.[1]
Parity	As reported in the Queensland Perinatal Data Collection - number of previous pregnancies resulting in live births or stillbirths, excluding the current pregnancy.[1]
Categories of Parity	For the purpose of this analysis, parity was categorised into two categories (parity nil to 2 or parity 3 or more) based on the median values for parity for these mothers (median 2 (IQR 1,4) [range 0-10].
Body Mass Index (BMI)	Weight in kilograms divided by height^2 in metres.[2]

	Characteristics of Mothers
Implausible weight and/or height values	Guidelines to identify implausible BMI values were not identified for mothers. Instead implausible weights and heights for mothers were identified based on information on weights and heights of participants of the National Nutrition Survey 1995.[3] In 1995, no participating girl aged 12 years or more weighed less than 35 kilograms or had a height measure less than 140cm and no participating girl/woman aged 16 years or more weighed less than 40 kilograms.[3] Among the mothers of the two present cohorts, none had body weights reported of less than 35 kilograms. Four heights of less than 140cm and nine weights of less than 40 kilograms for girls/women aged 16 years or over, were replaced with missing values. At the National Nutrition Survey 1995, 0.1% of women had a height of 180cm to 190cm and 0.2% had a body weight of 130 kilograms or more.[3] Among the mothers of the two present cohorts, eight had a height measurement 180cm and 190cm recorded which were replaced with missing vales. Eleven mothers had weights between 130 kg and 140 kg recorded. These values were considered plausible and retained.
Implausible Body Mass Index (BMI)	For women aged 18 years, the 3rd percentile of Body Mass Index for age is 17.2kg 4. As 3% of the reference population have Body Mass Index less than 17.2%, the definition of implausible low value for BMI was taken to be less than 16. Ten BMI values ranging from 14 up to 16 for mothers aged 18 years and over, were changed to missing. Two mothers under the age of 18 years had BMI values between 15 and 16 which were below but close to the third percentile BMI for age and therefore considered plausible.[4]
Smoking in pregnancy	As reported in the Queensland Perinatal Data Collection – any smoking recorded before and/or after 20 weeks gestation was classified as 'smoking in pregnancy'.

	Maternal health and nutrition indicators
Body Mass Index categories: mothers aged 18 years and over	BMI was categorised for mothers aged eighteen years and older, as defined by the Australian National Health and Medical Council (BMI < 18.5 underweight, 18.5 - <25.0 healthy weight, 25.0 - < 30.0 overweight, 30 or more obese).[2]
Body Mass Index categories: mothers aged less than 18 years	For mothers less than eighteen years of age, BMI was classified into the same categories (underweight, healthy weight, overweight, obese) using the criteria for girls aged between 2 years and eighteen years developed by Cole et al. (2007). These criteria have been used for child and adolescent participants of recent national surveys in Australia - the 2011-12 Australian National Health survey and the 2012-13 Australian Aboriginal and Torres Strait Islander Health survey and are the criteria recommended for analysis of survey data in the National Health Dictionary. [5, 6 7]
Date pregnancy commenced	Date pregnancy commenced was calculated by (date of birth of baby minus gestational age of baby)
Dates of pregnancy	Date pregnancy commenced up to date of birth of baby
First trimester	Date pregnancy commenced up to date pregnancy commenced plus 93 days
Second Trimester	Date pregnancy commenced plus 93 days up to date pregnancy commenced plus 186 days
Third Trimester	Date pregnancy commenced plus 186 days up to date of birth of baby
Anaemia in pregnancy	Haemoglobin < 110 g/L [8] as recorded on the Queensland Pathology Auslab electronic record system on a date during the pregnancy.
Anaemia in the third trimester	Haemoglobin < 110 g/L [8] as recorded on the Queensland Pathology Auslab electronic record system from the date pregnancy commenced plus 186 days up to date of birth of baby

	Maternal health and nutrition indicators
Iron deficiency	Defined as recommended by Pasricha et al. (2010) as Ferritin <15ug/L.[9] Ferritin levels are raised in the presence of infection and/or inflammation however insufficient information was available to adjust for inflammation (transferrin saturation, C-reactive protein) in mothers. Consequently, Ferritin levels >=15ug/L were classified as normal.
Pre-existing maternal diabetes	Diabetes defined using criteria as specified by the International Association of Diabetes and Pregnancy Study Groups, and by Queensland Health: fasting glucose levels of 7 mmol/L or more and/or glycated haemoglobin (hbA1c) levels of 6.5% or more. Diabetes was considered to be 'pre-existing' if a positive test result was reported before or during pregnancy. [8, 10]
Maternal gestational diabetes	Among mothers without pre-existing diabetes, gestational diabetes was defined as specified by the International Association of Diabetes and Pregnancy Study Groups - glucose tolerance test results: fasting glucose of 5.1 mmol/L up to 7mmol/L or one hour glucose 10.0 mmol/L or more, or two hour glucose 8.5 mmol/L or more. [8, 10]
Low Red Cell Folate (RCF)	Defined as per Queensland Health Pathology - measurement result <356 nmol/L. [11]
Low Vitamin B12	Defined as per Queensland Health Pathology - measurement result <133 pmol/L. [11]
Hypertension	Defined as per Gabb et al. (2016) and by Queensland Health (2015) - systolic blood pressure equal to or greater than 140mm Hg and/or diastolic blood pressure equal to or greater than 90mm Hg 12, 13.

	Children at birth
Live born	Baby with gestational age of at least 20 weeks or at least 400g birth weight, shows signs of life at birth.[1]
Gestational age at birth	Best clinical estimate of duration of pregnancy at birth, expressed in completed weeks.[7]
Prematurity	Gestational age at birth of less than 37 weeks. [14]
Low birth weight	Birth weight of a live born baby less than 2,500g. [14]
Macrosomia	Birth weight of 4,000g or more.[14]
High Macrosomia	Birth weight of 4,500g or more.[14]
Z-score for birth weight for gestational age	Birth weight z-scores adjusted for sex and gestational age calculations were based on the International Standards for Size at Birth for newborns. [15]

	Children birth up to age 5 years
Anaemia 6 - <12 months	Haemoglobin level <105 g/L. [16]
Anaemia 12 to 23 months	Haemoglobin level <110 g/L. [16]
Early Childhood Anaemia (ECA)	Anaemia between age 6 months and 23 months.
Feeding to 4 months	Child health check records on Ferret for feeding to age four months showed: breast feeding only or infant formula only or both breast feeding and infant formula or missing value.
Weight for Age z-score	World Health Organization Child Growth Standards were used to calculate z-scores for weight for age at first weight between age 4 to 6 months using the STATA 'zscore06' module.[17, 18]
Implausible weight values	World Health Organization criteria to identify implausible weight for age (excluding birth weights) for children under age five years based on z-scores – weights were identified as implausible if they resulted in a weight for age z-score less than minus 6 or greater than plus 5. These criteria were applied to identify implausible weight measurements n = 215 (1.4%) up to age 60 months which were changed to missing.[18]
Z-score change	Weight for age z-score at first weight at age 4 to 6 months less birth weight z-score. [15, 17, 19]

Supplementary Table 4.2 References

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Supplementary Table 4.3

"Missing-ness" of characteristics in analysis of risk factors for early childhood anaemia in 708 Aboriginal children from North Queensland. Data was collected in two cohorts: Cohort 1 "2009-2010 cohort" n=407 (C1); Cohort 2 "Cape York cohort" n=301 (C2).

	Number of missing values (%)	**Cohort**	**Z-score of weight gain difference birth to 4-6 m**	**Feeding method birth to 4-6 m**	**Parity**	**BMI categories mother**	**Diabetes during pregnancy**	**Anaemia during pregnancy**	**Low folate level in mother**	**Low B12 in mother**
Z-score of weight gain difference birth to 4-6 m	181 (25.6%)	P=0.056	/	P<0.001	P=0.638	P=0.576	P=0.103	P=0.755	P=0.115	P=0.317
Feeding method birth to 4-6 m	164 (23.2%)	P=0.001; C1 more M*		/	P=0.340	P=0.101	P=0.003	P=0.501	P=0.346	P=0.402
Parity	233 (32.9%)	P=0.511			/	P=0.960	P=0.570	P=0.061	P=0.007	P=0.013
BMI categories mother	227 (32.1%)	P<0.001; C2 more M				/	P<0.001	P<0.001	P=0.748	P=0.534

	Number of missing values (%)	Cohort	Z-score of weight gain difference birth to 4-6 m	Feeding method birth to 4-6 m	Parity	BMI categories mother	Diabetes during pregnancy	Anaemia during pregnancy	Low folate level in mother	Low B12 in mother
Diabetes during pregnancy	254 (35.9%)	P<0.001; C2 more M					/	P<0.001	P=0.614	P=0.545
Anaemia during pregnancy	36 (5.1%)	P<0.001; C2 more M						/	P=0.001	P=0.003
Low folate level in mother	550 (77.7%)	P=0.063							/	P<0.001
Low B12 in mother	577 (81.5%)	P=0.190								/
Antenatal care 5+	1 (0.1%)	/								
Smoking during pregnancy	5 (0.7%)	P=0.655**								

Footnotes
p-values are results of Chi-square test statistics and **Fisher's exact test comparing the occurrences of missing values. *"M" stands for missing values.

Supplementary Table 4.4
Early childhood anaemia among two cohorts of Aboriginal and Torres Strait Islander children and their mothers in Far North Queensland; comparisons of study participant numbers with census information.

Supplementary Table 4.4a.
Comparisons of numbers of Cape York cohort child participants with Census 2006 population figures (Australian Bureau of Statistics – Community Profile Series 2006♦).

Census 2006	**Cape York remote communities**	**2006 age 0-<1year (Indigenous)**
IARE 12011	Kowanyama	22
IARE 12009	Pormpuraaw	7
IARE 12007	Aurukun	20
IARE 12005	Napranum	23
IARE 12019	Mapoon	6
IARE 12017	Lockhart River	15
IARE 12015	Hope Vale	17
IARE 12013	Wujal Wujal	10
ILOC 1202501	Coen	5
Cook Shire - SSC 36537	Laura	0
Births in 2006		125
Estimated births 2006 – 2008 (3 x 125)		**375**
Cape York cohort children with PDC record of birth and Ferret record		**380**

Footnotes: IARE - Indigenous Area; ILOC - Indigenous Location; SSC – State Suburbs; IREG – Indigenous Region

Supplementary Table 4.4b.
Comparisons of numbers of 2009 and 2010 cohort child participants with Census 2011 population figures (Australian Bureau of Statistics – Community Profile Series 2011[•]).

Region	ABS community profile code	Locality	Census 2011 A&TSI <1yr
Cape York	IARE303001	Aurukun	18
Torres Region	ILOC30700302	Badu	28
Torres Region	350105781	Bamaga	27
Torres Region	ILOC30700201	Boigu	3
Cape York	ILOC30300202	Coen	8
Cape York	ILOC30300301	Cooktown	5
Torres Region	ILOC30700202	Dauan	3
Torres Region	ILOC30700501	Erub	6
Cape York	ILOC30300401	Hope Vale	18
Torres Region	ILOC30700102	Horn Island	7
Torres Region	ILOC30700401	Iama Island	8
Torres Region	ILOC30300802	Injinoo	16
Cairns & Hinterland	ILOC30801502	Jumbun	3
Cape York	IARE303005	Kowanyama	22
Torres Region	ILOC30700302	Kubin	3
Cairns & Hinterland	SSC30911	Kuranda*	17
Cape York	SSC30942	Laura**	1
Cape York	IARE303006	Lockhart River	6
Torres Region	ILOC30700303	Mabuiag	3
Cape York	ILOC30300701	Mapoon	0
Torres Region	SSC31025	Masig***	7
Torres Region	ILOC30700502	Mer	4
Cairns & Hinterland	ILOC30200301	Mossman	5

Region	ABS community profile code	Locality	Census 2011 A&TSI <1yr
Cape York	ILOC30300702	Napranum	18
Torres Region	ILOC30300803	New Mapoon	11
Cape York	IARE303009	Pormpuraaw	11
Torres Region	ILOC30700402	Poruma	0
Torres Region	ILOC30700203	Saibai	11
Torres Region	ILOC30300804	Seisa	3
Torres Region	ILOC30700304	St Pauls, Moa	7
Torres Region	ILOC30700105	TI-TRAWQ	16
Torres Region	ILOC30700503	Ugar	0
Torres Region	ILOC30300805	Umagico	6
Torres Region	ILOC30700403	Warraber	6
Cape York	ILOC30300703	Weipa	16
Cape York	ILOC30201002	Wujal Wujal	0
Cairns & Hinterland	IARE302011	Yarrabah	63
Census 2011 enumeration babies aged 0-<1yr in 2011			386
Estimated number born 2009&2010 (386 x 2)			**772**
2009 and 2010 cohort children with PDC record of birth and Ferret record			**775**

Footnotes:

IARE - Indigenous Area; ILOC - Indigenous Location; SSC – State Suburbs; IREG – Indigenous Region
* derived from n = 87 aged 0-4 years
** derived from n = 3 aged 0-4 years
*** derived from n = 37 aged 0-4 years

♦**Australian Bureau of Statistics Community profiles**
http://www.abs.gov.au/websitedbs/censushome.nsf/home/communityprofiles?opendocument&navpos=230

Supplementary Table 4.5

Far North Queensland Aboriginal and/or Torres Strait Islander children with a Ferret record (n = 957): comparing those seen by health services at age six to 23 months (n = 904) with those not seen (n = 53).

Child characteristic	All children with a Ferret record (n=957)		Child seen by health service between 6 -< 24 months				p values (chi^2 test)
			Yes (n=904, 94.6%)		No (n=53, 5.6%)		
	n	(%)	n	(%)	n	(%)	
Male	501	(52.4%)	473	(52.3%)	28	(52.8%)	0.943
Premature	105	(11.0%)	98	(10.8%)	7	(13.2%)	0.592
Birth weight category							
Low birth weight	100	(10.4%)	97	(10.7%)	3	(5.7%)	0.218 (nptrend)
Normal	787	(82.2%)	742	(82.1%)	45	(84.9%)	
High	70	(7.3%)	65	(7.2%)	5	(9.4%)	
Region of residence							
Cairns and Hinterland	97	(10.1%)	81	(9.0%)	16	(30.2%)	<0.001
Cape York	483	(50.5%)	475	(52.5%)	8	(15.1%)	
Torres Strait and Northern Peninsula Area	377	(39.4%)	348	(38.5%)	29	(54.7%)	
Teenage mother (<20 years)	211	(22.0%)	200	(22.1%)	11	(20.8%)	0.815
Mother resident in SEIFA Level 1	824	(86.1%)	782	(86.5%)	42	(79.2%)	0.138
Mother smoked in pregnancy (n = 952)	582	(61.1%)	550	(61.2%)	32	(60.4%)	0.907

Supplementary Table 4.6

Far North Queensland Aboriginal and/or Torres Strait Islander children with a Ferret record seen by health services at age six to 23 months (n = 904) - comparing those with at least one haemoglobin measure (n = 708) with those with no haemoglobin measure (n = 196) at age six to 23 months.

Child characteristic	All children with a Ferret record seen by health services (n=904)		Haemoglobin measured between 6 -< 24 months				p values (chi^2 test)
			Yes (n=708, 78.3%)		No (n=196, 21.7%)		
	n	(%)	n	(%)	n	(%)	
Male	473	(52.3%)	363	(51.3%)	110	(56.1%)	0.229
Premature	98	(10.8%)	82	(11.6%)	16	(8.2%)	0.173
Birth weight category							0.087 (nptrend)
Low birth weight	97	(10.7%)	81	(11.4%)	16	(8.2%)	
Normal	742	(82.1%)	580	(81.9%)	162	(82.7%)	
High	65	(7.2%)	47	(6.6%)	18	(9.2%)	
Region of residence							<0.001
Cairns and Hinterland	81	(9.0%)	56	(7.9%)	25	(12.8%)	
Cape York	475	(52.5%)	442	(62.4%)	33	(16.8%)	
Torres Strait and Northern Peninsula Area	348	(38.5%)	210	(29.7%)	138	(70.4%)	

Child characteristic	All children with a Ferret record seen by health services (n=904)		Haemoglobin measured between 6 -< 24 months				p values (chi² test)
			Yes (n=708, 78.3%)		No (n=196, 21.7%)		
	n	(%)	n	(%)	n	(%)	
Teenage mother	200	(22.1%)	163	(23.0%)	37	(18.9%)	0.216
Mother resident in SEIFA Level 1	782	(86.5%)	620	(87.6%)	162	(82.7%)	0.075
Mother smoked in pregnancy (n = 899)	550	(61.2%)	439	(62.0%)	111	(56.6%)	0.140

Supplementary Table 4.7

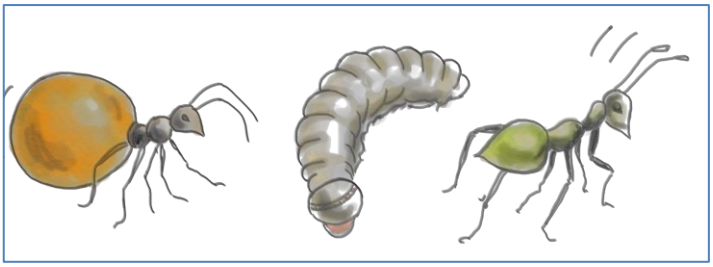
Risk factors for Early Childhood Anaemia (anaemia between six and 23 months) among Aboriginal and Torres Strait Islander children of Far North Queensland (n = 708): Results of multi variable analysis using region of residence of mother instead of ethnicity in imputed data model. (all other variables as in Table 3).

	Complete case analysis N=337					**Imputed data analysis N=708**			
Characteristic	Anaemia N=208 (61.7%)	No Anaemia N=129 (38.3%)	Odds-ratio (95% CI)^	p-value	Number of missing values (%)	Anaemia N=434 (61.3%)	No Anaemia N=274 (38.7%)	Odds-ratio (95% CI)^	p-value
Residence of mother					0				
Cape York	163 (78.4%)	62 (48.1%)	1			318 (73.3%)	124 (45.3%)	1	
Cairns & Hinterland	6 (2.9%)	5 (3.9%)	0.38 (0.26, 0.57)	P<0.001		29 (6.7%)	27 (9.9%)	0.39 (0.20, 0.76)	P=0.005
Torres Strait & NPA	39 (18.8%)	62 (48.1%)	0.24 (0.09, 0.65)	P=0.005		87 (20.1%)	123 (44.9%)	0.27 (0.12, 0.64)	P=0.003

Foreword Chapter 5 (Results 3)

In Chapter 5, I present the findings of this research in respect of the association between anaemia at age 6-23 months and the early childhood developmental indicators of those children who were assessed in their first year of full-time school during the Australian Early Development Censuses of 2012 or 2015.

The information presented in this chapter has been submitted for publication in *Nutrition and Dietetics*; at the time of writing, this article has been accepted for publication but is not yet published.



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Chapter 5 Early Childhood Anaemia More Than Doubles the Risk of Developmental Vulnerability at School Age Among Aboriginal and Torres Strait Islander Children of Remote Far North Queensland: Findings of a Retrospective Cohort Study

5.1 Abstract

Aims: Early childhood anaemia - anaemia between age six and 23 months - due to iron deficiency is associated with persistent with persistent detrimental effects child development. This study investigates the association of early childhood anaemia with indicators of child development at school-age among children of remote Aboriginal and Torres Strait Islander communities of Far North Queensland

Methods: The triennial Australian Early Development Census (AEDC) encompasses five domains of early childhood development - physical health and wellbeing, social competence, emotional maturity, language and cognitive skills (school-based), communication skills and general knowledge. AEDC 2012 and 2015 assessments

were linked with health information for children and their mothers from remote Aboriginal and Torres Strait Islander communities of Far North Queensland.

Results: AEDC assessments were available for 250 children who had measurements of haemoglobin recorded at age 6-23 months. More children who had had early childhood anaemia (n=66/143, 46.2%, [37.9%, 54.4%]) were developmentally vulnerable on two or more domains compared to those who had not been anaemic (n=25/107, 23.4% [15.2%, 31.5%], $p < 0.001$). Multivariable analysis confirmed that early childhood anaemia more than doubled the risk of developmental vulnerability (OR 2.2 [1.1, 4.3] $p = 0.020$) at school age.

Conclusions: Early childhood anaemia is a risk factor for developmental vulnerability at school-age among Aboriginal and Torres Strait Islander children of remote Far North Queensland.

Implications: *Where anaemia is prevalent, interventions promoting good nutrition in early life combined with multi-micronutrient food fortification, are recommended by the World*

Health Organization. These interventions are effective in prevention and treatment of early childhood anaemia, and may improve early childhood development and subsequent educational achievement. Such interventions should be considered for implementation in remote Far North Queensland.

Keywords: anaemia; anemia; infant; child; micronutrients; development

5.2 Introduction

Good nutrition in the first thousand days of life – from conception, through pregnancy to age two years - supports the rapid neurodevelopment of early life that provides the scaffolding for subsequent child development.[1] Iron is particularly important during critical phases of neurodevelopment.[1, 2] Iron deficiency in early life is associated with persistent deficits in cognitive and behavioural performance.[2, 3] Iron deficiency anaemia is a late stage of iron deficiency; as detrimental effects can occur prior to anaemia developing, prevention of anaemia is important for optimal neurodevelopment.[1]

Anaemia - defined as low haemoglobin – among Aboriginal and Torres Strait Islander women in pregnancy and their children in early life, is prevalent in Far North Queensland and elsewhere in remote northern Australia.[4-8] Anaemia can be nutrition-related – other possible causes are chronic infections and genetic conditions.[9] Anaemia in the first thousand days is usually caused by iron deficiency due to high iron requirements for rapidly increasing blood volume and tissue growth.[1, 2]

The Australian Early Development Census (AEDC) is a national census of early childhood development, conducted every three years since 2009.10 Each child in the first year of full time school is assessed by his/her teacher on five domains of early childhood development; physical health and wellbeing, social competence, emotional maturity, language and cognitive skills (school-based), communication skills and general knowledge.[10] These AEDC domains are predictive of outcomes in health, well-being and academic success in later life.[10] In Australia, AEDC results have been shown to predict subsequent National Assessment of Performance Literacy and Numeracy (NAPLAN) scores for numeracy and reading.[11]

The 2015 AEDC census with 302,003 child participants found that 22.0% were developmentally vulnerable – scoring below the tenth centile - on one or more domains (DV1) and 11.1% developmentally vulnerable on two or more domains (DV2). More boys were developmentally vulnerable than girls.[10] Studies in South Australia and the Northern Territory identified perinatal factors associated with developmental vulnerability at school entry; smoking in pregnancy; anaemia of mothers; low birth weight; prematurity among Aboriginal and non-Aboriginal children.[12, 13]

Here we report on the association of early childhood anaemia, defined as a child ever having anaemia between age 6-23 months, with AEDC assessment results among Aboriginal and Torres Strait Islander children of remote Far North Queensland.

5.3 Methods

This retrospective cohort study used linked information for two cohorts of children and their mothers - the Cape York cohort and the 2009-2010 cohort. The Cape York cohort included children born between 2006 and 2008, participants in a previous review of child growth in remote Cape York communities. The 2009-2010 cohort included children born to Aboriginal and/or Torres Strait Islander mothers in 2009 or 2010 in Far North Queensland. Only the first child born to each mother between 2006 and 2010 was included to ensure independence of events for statistical analysis (Figure 5.2).

Information was sourced from three Queensland Health data collections; 1) Queensland Pathology Services data collection (Auslab) 2) Queensland Perinatal Data Collection (PDC) 3) the Queensland Health community health electronic record system - Ferret - used in Far North Queensland remote Aboriginal and Torres Strait Islander communities (Figure 5.1). Information recorded on Ferret includes results of routine child haemoglobin measurements from age six months. Health information for individual children and their mothers was linked to the child's assessment from AEDC 2012 or AEDC 2015. The final linked de-identified dataset was provided to researchers in May 2017. A full description of this linkage process is described elsewhere.[14] Supplementary Table 5.1 provides more information on these data collections.

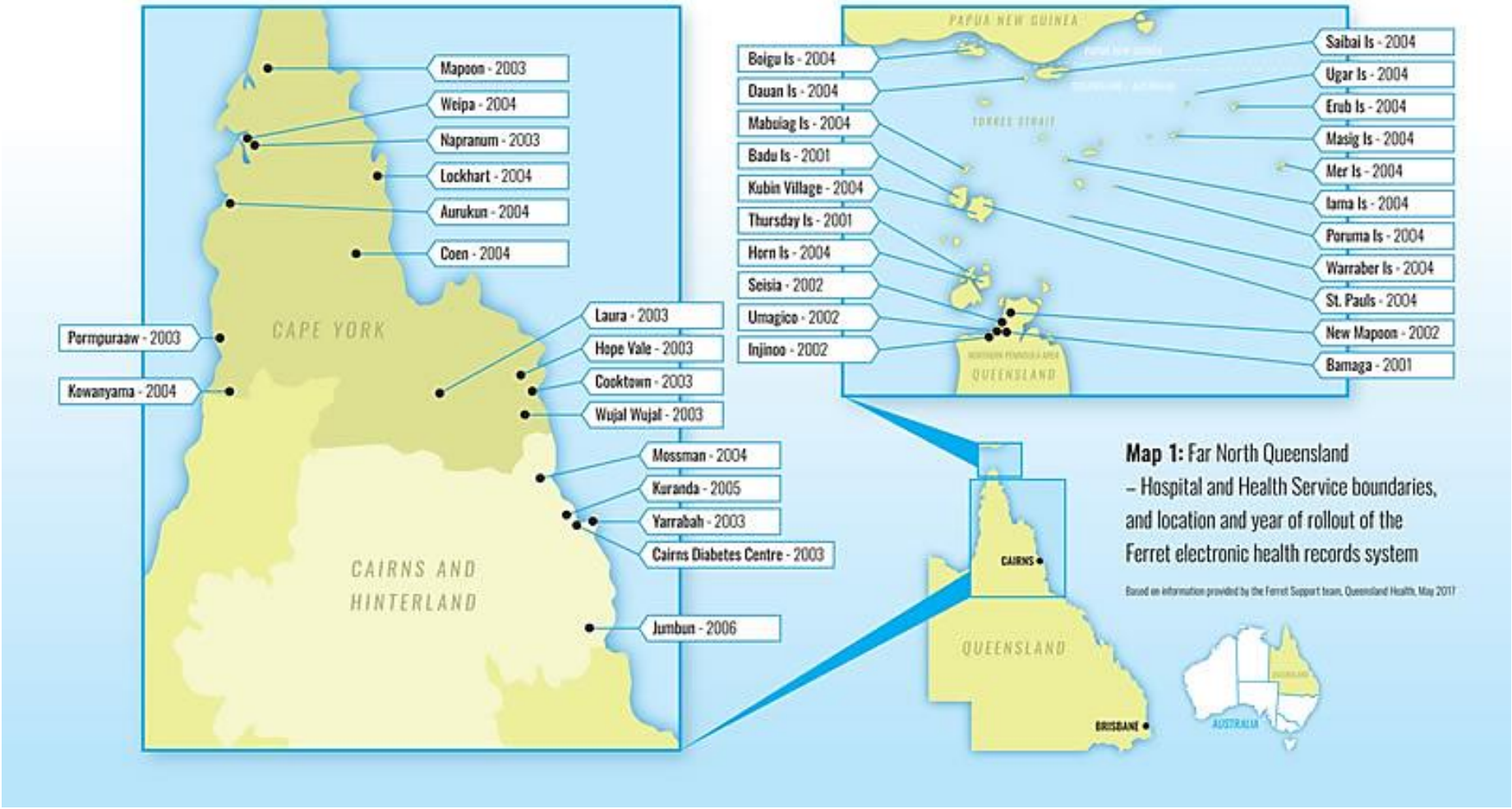

Figure 5.1 Map 1: Far North Queensland – location and year of rollout of the Ferret electronic record system. Based on information provided by the Queensland Health Ferret Support Team, May 2017.
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5.3.1 Ethics approval

Ethics approval was granted by Queensland Health Far North Queensland Human Research Ethics Committee (HREC/15/QCH/50-980) in June 2015. In February 2016, approval under the Queensland Public Health Act 2005 was granted by the Director-General of Queensland Health. In September 2016, approval was granted by the Australian Government Department of Education and Training Australian to access the Australian Early Development Census data collection. The complete linked de-identified data was provided to the research group in May 2017.

5.3.2 Study variables and definitions

Information on the outcome variables - developmental vulnerability – was sourced from the AEDC data collection.[10] Criteria for categories of developmental status (on track, developmentally at risk, developmentally vulnerable) are based on the first AEDC in 2009; children scoring below the AEDC 2009 tenth centile for each domain are categorised as developmentally vulnerable for that domain. Children with scores below the tenth centile for one or more of the five AEDC domains are categorised as DV1. Children with scores below the tenth centile for two or more domains are categorised as DV2[10] (Supplementary Table 5.2).

Information on the characteristics of children and mothers were sourced from the health service data collections. Anaemia in early childhood was defined using the Queensland Health age-specific criteria; at least one haemoglobin level recorded below 105 g/L from 6-11 months, and/or below 110g/L from 12-23 months.[15]

Some characteristics are as recorded on health service data collections: mother's usual residence, ethnicity, parity, smoking in pregnancy; child's sex, gestational age at birth, birth weight, method of birth. Criteria to define derived variables including maternal age, body mass index (BMI), anaemia before and during pregnancy, insufficient red cell folate levels (folate status less than optimal for women of reproductive age to prevent neural tube defects [16, 17] child's prematurity and birth weight category are detailed in Supplementary Table 5.2. Birth weight z-scores for babies with gestational age of 33 weeks or more, were calculated using the INTERGROWTH-21ST Neonatal Size Calculator.[18, 19]

Australian Bureau of Statistics ranks Statistical Local Areas by deciles of relative socio-economic advantage and disadvantage.[20] A ranking of '1' indicates greatest relative disadvantage while a ranking of '10' indicates greatest relative advantage. Mothers were allocated a Socio-Economic Index for Areas (SEIFA 2011) rank according to usual place of residence.

5.3.3 Statistical analysis

Analysis was conducted using Stata version 13 (StataCorp, Lakeway Drive, College Station, Texas). Categorical variables were described using absolute and relative frequencies. The distributions of numerical variables were assessed; symmetrically distributed numerical characteristics were described using mean values and standard deviations (SDs); numerical values with a skewed distribution were described using median and inter-quartile ranges (IQR).

The main outcome variables for bivariate analysis were; 1) developmentally vulnerable for one or more of the five domains - DV1; and 2) developmentally vulnerable for two or more of the five domains - DV2. The main outcome variables were presented with 95% confidence interval (95% CI).

The following characteristics of children and their mothers were considered during bi- and multivariable analyses: sex; birthing method (non-instrumental vaginal, instrumental vaginal, caesarean section); gestational age at birth; premature or not; birth weight; feeding method to age 4 months (only breast milk, only infant formula, both breast milk and formula); child had anaemia at age 6-23 months or not; ethnicity of mother (Aboriginal, Torres Strait Islander, both); region of residence of mother; SEIFA category for residence of mother; maternal age; BMI category of mother (underweight, normal weight, overweight, obese); categories of parity (0-2, >=3); smoking during pregnancy; diabetes during pregnancy; mother had insufficient red cell folate (RCF) level before or during pregnancy; mother anaemic both before and during pregnancy.

Developmental vulnerability was compared by these characteristics of the children and their mothers, using bivariate logistic regression analyses. In addition, the association of developmental vulnerability for each domain was assessed for; mother anaemic both before

and during pregnancy; smoking during pregnancy; early childhood anaemia, using Pearson's Chi-square tests.

Multivariable logistic regression analyses were conducted to identify independent risk factors for children considered developmentally vulnerable on two or more domains (DV2) for the complete case analysis. Backward and forward stepwise modelling procedures were initially conducted to establish a basic multivariable model. Characteristics that were not part of the basic model were assessed for potential confounding effects. A confounder was assumed to be a variable that changed estimates of characteristics in the basic model by 10% or more.[21]

Univariate multiple imputation was conducted using Stata's MI commands for missing values for one characteristic: mother anaemic both before and during pregnancy (n=29). Other characteristics with missing values, including feeding method, parity, BMI of mother, diabetes in pregnancy, and insufficient RCF levels of mother were not imputed because these variables had shown no statistically significant influence on the main outcome variables during bi- and multivariable analyses.

The occurrence of missing values of mother anaemic both before and during pregnancy (n=29) was found unrelated to DV2 using Pearson's Chi-square test. The pattern of missing values was assessed and judged to be "missing at random".[22] Logistic regression was used for imputation. Imputation models were based on variables with nil missing data; birth weight of baby; smoking during pregnancy; early childhood anaemia; sex of baby; gestational age of baby; AEDC developmental assessment; birthing method; ethnicity of mother, age of mother, SEIFA index; residential region; and cohort. Twenty imputed data sets were created. Multivariable logistic regression analyses were conducted to identify independent risk factors for DV2 for imputed data.

Results of multivariable models for complete case and imputed data analyses are presented as odds ratios (OR) and 95% confidence intervals. P values of less than 0.05 were considered statistically significant. The authors used the STROBE checklist for cohort studies to guide the preparation of this paper.

5.4 Results

Ferret longitudinal health records were available for 1,155 children of whom 957 were the first child born to his/her mother in the cohort years (Figure 5.2). Of these 957 children, 708 children had a record of haemoglobin measurement at age 6-23 months. Just over one third (35.3%, n = 250) of the 708 children also had a record of AEDC assessment. More than half (58.0%; 95% CI 51.6%, 64.2%) of these 250 children were assessed as DV1 and approximately one third (36.4%; 95% CI 30.4%,42.7%) as DV2 (Table 5.1).

Bivariate analysis showed developmental vulnerability was significantly more prevalent among children who had had early childhood anaemia (DV2 n=66/143, 46.2% [95%CI 37.9%, 54.4%]) compared to those who had not been anaemic (DV2 n=25/107, 23.4% [95%CI 15.2%, 31.5%] $p < 0.001$). Developmental vulnerability was significantly more prevalent among boys compared to girls; children of mothers who were anaemic both before and during pregnancy; children of mothers who smoked in pregnancy. These effects were seen for both the DV1 and the DV2 categories (Tables 5.1 and 5.2). Children of Torres Strait Islander mothers were significantly less likely to be categorised as either DV1 or DV2 compared to the children of other Indigenous mothers (Table 5.2).

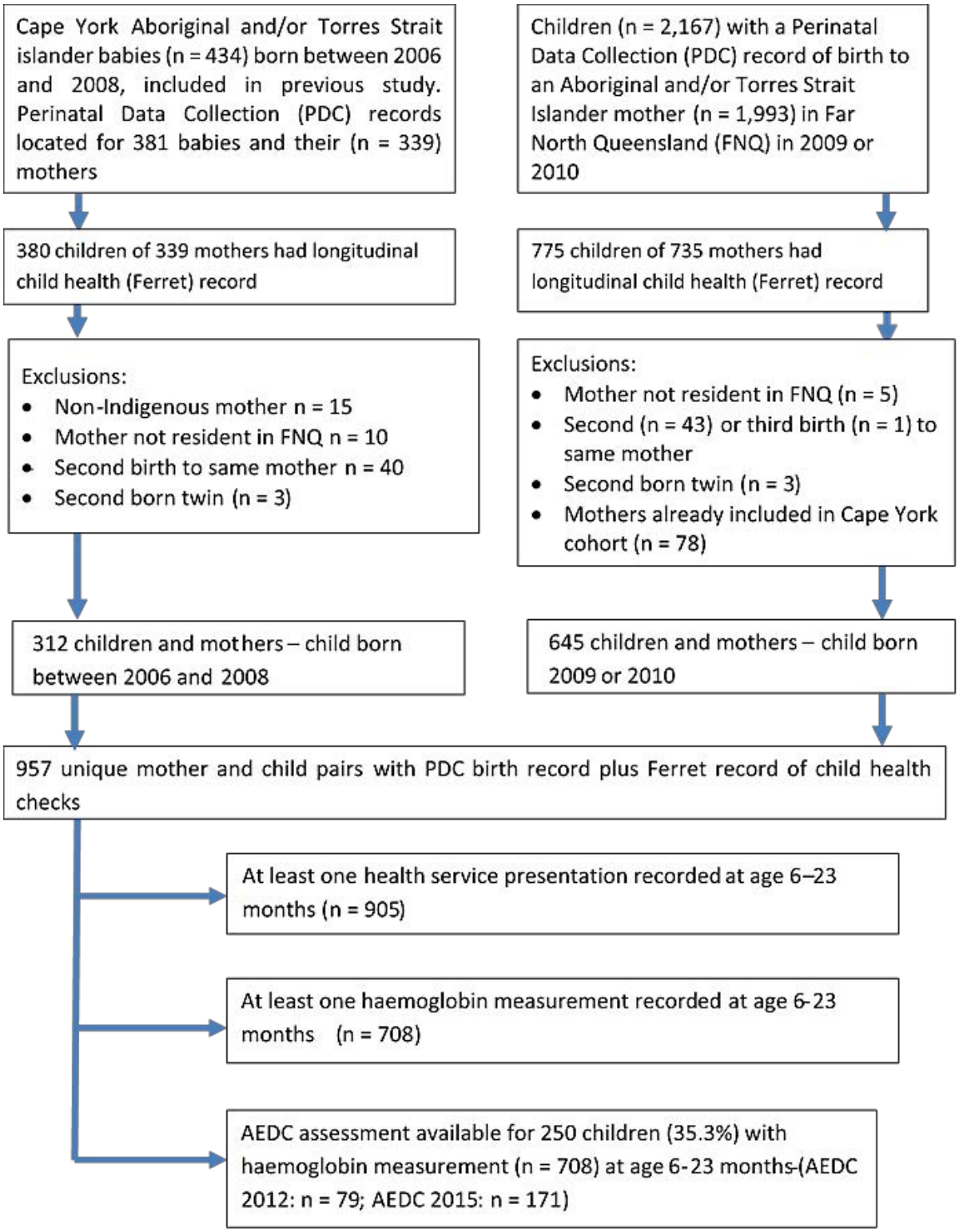

Figure 5.2 Flow diagram – investigating the association between Early Childhood Anaemia and Australian Early Development Census indicators - data availability and exclusions for two cohorts of Aboriginal and Torres Strait Islander children and their mothers in Far North Queensland.

Table 5.1

Developmental vulnerability (in lower 10th percentile of AEDC assessment score at first year of full-time school) in one or more domains (DV1) and in two or more domains (DV2) by characteristics of the child – bivariate analysis (logistic regression).

Table 5.1 – Part A

Characteristics of children	Number	AEDC- DV1(Y) n = 145 (58.0%)	p values (DV1 logistic regression)	AEDC- DV2 (Y) n = 91 (36.4%)	p values (DV2 logistic regression)
Sex n = 250					
boys	132	88 (66.7%) [58.5%, 74.8%]	p = 0.004*	62 (47.0%) [38.3%, 55.6%]	p < 0.001*
girls	118	57 (48.3%) [39.2%, 57.5%]		29 (24.6%) [16.7%, 32.5%]	
Birth weight category n = 250					
low birth weight	31	19 (61.3%) [43.1%, 79.5%]	p = 0.713	n =<15	p = 0.401
normal birth weight	199	115 (57.8%) [50.9%, 64.7%]	base	68 (34.2%) [27.5%, 40.8%]	base
♦macrosmic (>4000g)	20	n = <15	p = 0.810	n =<15	p = 0.164
Premature birth					
♦child - premature birth	32	20 (62.5%) [44.8%, 80.2%]	p = 0.581	n =<15	p = 0.356
child - full term birth	218	125 (57.3%) [50.7%, 64.0%]		77 (35.3%) [28.9%, 41.7%]	

Table 5.1 – Part A					
Characteristics of children	**Number**	**AEDC- DV1(Y) n = 145 (58.0%)**	**p values (DV1 logistic regression)**	**AEDC- DV2 (Y) n = 91 (36.4%)**	**p values (DV2 logistic regression)**
Birth method n = 250		5.			
vaginal	172	99 (57.6%) [50.1%, 65.0%]	base	67 (39.0%) [32.0%, 46.3%]	base
♦vaginal instrumental	n=<15	n=<15	p = 0.845	n=<15	p = 0.186
caesarian	67	40 (59.7%) [47.6%, 71.8%]	p = 0.763	22 (32.8%) [21.3%, 44.4%]	p = 0.380
Feeding method - birth to age 4 months n = 189					
breast milk only	83	48 (57.8%) [47.0%, 68.7%]	base	34 (41.0%) [30.2%, 51.8%]	base
♦infant formula only	25	17 (68.0%) [48.3%, 87.7%]	p = 0.365	n =<15	p = 0.657
both breast milk and infant formula	81	48 (59.3%) [48.3%, 70.2%]	p = 0.853	30 (37.0%) [26.3%, 47.8%]	p = 0.606

Table 5.1 – Part A					
Characteristics of children	**Number**	**AEDC- DV1(Y) n = 145 (58.0%)**	**p values (DV1 logistic regression)**	**AEDC- DV2 (Y) n = 91 (36.4%)**	**p values (DV2 logistic regression)**
Early Childhood Anaemia (age 6-23 months) n= 250		5.			
Yes	143	92 (64.3%) [56.4%, 72.3%]	p = 0.019*	66 (46.2%) [37.9%, 54.4%]	p <0.001*
No	107	53 (49.5%) [39.9%, 59.2%)		25 (23.4%) [15.2%, 31.5%]	

Footnotes:

♦AEDC require that results relating to cell sizes of 15 or less are not provided to protect confidentiality
Categorical variables are shown as absolute and relative frequencies (percentages) with [95% confidence intervals] – child sex, method of birth, birth weight category, premature birth, feeding method, early childhood anaemia.
*p value less than 0.05

Table 5.1 – Part B

Characteristics of children	DV1 = No n = 105	DV1 = Yes n = 145	p values (logistic regression)	DV2 = No n = 159	DV2 = Yes n = 91	p values (logistic regression)
Birth weight g mean (SD) [95% CI]	3234 (654) [3108, 3361]	3161 (615) [3060, 3262]	p = 0.365	3181 (614) [3085, 3277]	3210 (664) [3072, 3348]	p = 0.725
Z-score birthweight adjusted for sex and gestational age mean (SD) [95%CI] {n}	+0.236 (1.1) [+0.2, +0.45] {n = 102}	+0.236 (1.2) [-2.4, +2.9] {n = 143}	p = 0.500	+0.13 (1.1) (-0.043, +0.30] {n = 156}	+0.27 (1.2) [+0.03, +0.52) {n = 89}	p = 0.381
Gestational age at birth weeks median (IQR) [95%CI]	39 (38,40) [39,40]	39 (37,40) [38,29]	P = 0.166	39 (38,40) [39, 39.4]	39 (37,40) [38,39]	p = 0.140

Footnotes:

Symmetrically distributed numerical variables are shown as mean (Standard Deviation) and [95% confidence intervals] – birth weight, z-score birthweight
Numerical values with a skewed distribution are shown as median and inter-quartile range (IQR) and [95% confidence intervals] – gestational age at birth
*p value less than 0.05

Table 5.2

Developmental vulnerability (in lower 10th percentile of AEDC assessment score at first year of full-time school) in one or more domains (DV1) and in two or more domains (DV2) by characteristics of the mothers – bivariate analysis (logistic regression).

Table 5.2 - Part A

Characteristics of mothers n = 250 unless otherwise specified	Number with that characteristic	AEDC-DV1 (Y) n = 145 (58.0%)	p values (DV1 - logistic regression)	AEDC-DV2 (Y) n = 91 (36.4%)	p values (DV2 - logistic regression)
♦**Ethnicity of mother**					
Aboriginal	132	91 (68.9%) [60.9%, 76.9%]	base	62 (47.0%) [38.3%, 55.6%]	base
Torres Strait Islander	97	42 (43.3%) [33.3%, 53.3%]	p < 0.001*	25 (25.8%) [16.9%, 34.6%]	p = 0.001*
Aboriginal and Torres Strait Islander	21	n =<15	p = 0.288	n =<15	p = 0.023*
♦**Mother's region of residence**					
Cairns and Hinterland	19	n =<15	p = 0.218	n =<15	p = 0.135
Cape York	134	90 (67.2%) [59.1%, 75.2%]	base	60 (44.8%) [36.2%, 53.3%]	base
Torres Strait	97	45 (46.4%) [36.3%, 56.5%]	p = 0.002*	26 (26.8%) [17.8%, 35.8%]	p = 0.006*

Table 5.2 - Part A

Characteristics of mothers	Number with that characteristic	AEDC- DV1 (Y) n = 145 (58.0%)	p values (DV1 - logistic regression)	AEDC- DV2 (Y) n = 91 (36.4%)	p values (DV2 - logistic regression)
Mother's age when child born - quartiles					
Teenager - younger than 20 years	52	33 (63.5%) [49.9%, 77.0%]	p = 0.125	17 (32.7%) [19.5%, 45.9%]	p = 0.824
20 to 23 years	65	32 (49.2%) [36.7%, 61.7%]	base	20 (30.8%) [19.2%, 42.9%]	base
24 to 30 years	69	39 (56.5%) [44.5%, 68.5%]	p = 0.398	25 (36.2%) [24.6%, 47.9%]	p = 0.504
> 30 years	64	41 (64.1%) [52.0%, 76.1%]	P = 0.908	29 (45.3%) [32.8%, 57.8%]	p = 0.090
♦SEIFA – mother's usual locality					
mother lives in SEIFA 1 locality	219	128 (58.5%) [51.9%, 65.0%]	p = 0.703	80 (36.5%) [30.1%, 43.0%]	p = 0.910
mother does NOT live in SEIFA 1 locality	31	17 (54.8%) [36.3%, 73.4%]		n =<15	
Mother's parity - cohort pregnancy n = 173					
parity 0 - 2	92	58 (63.0%) [53.0%, 73.1%]	p = 0.859	38 (41.3%) [31.1%, 51.6%]	p = 0.810
parity 3 or more	81	50 (61.7%) [50.9%, 72.5%]		32 (39.5%) [28.6%, 50.4%]	

Table 5.2 - Part A					
Characteristics of mothers	**Number with that characteristic**	**AEDC- DV1 (Y) n = 145 (58.0%)**	**p values (DV1 - logistic regression)**	**AEDC- DV2 (Y) n = 91 (36.4%)**	**p values (DV2 - logistic regression)**
Mother's Body Mass Index n = 161					
under or healthy weight	57	36 (63.2%) [50.2%, 76.1%]	base	23 (40.4%) [27.2%, 53.5%]	base
overweight	42	23 (54.8%) [39.1%, 70.5%]	p = 0.401	13 (31.0%) [16.4, 45.5%]	p = 0.338
obese	62	30 (48.4%) [35.6%, 61.2%]	p = 0.107	21 (33.9%) [21.8%, 46.0%]	p = 0.465
Smoking in pregnancy					
Yes	153	101 (66.0%) [58.4%, 73.6%]	p = 0.001*	65 (42.5%) [34.7%, 50.4%]	p = 0.013*
No	97	44 (45.4%) [35.3%, 55.4%]		26 (26.8%) [17.8%, 35.8%]	

Table 5.2 - Part A					
Characteristics of mothers	**Number with that characteristic**	**AEDC- DV1 (Y) n = 145 (58.0%)**	**p values (DV1 - logistic regression)**	**AEDC- DV2 (Y) n = 91 (36.4%)**	**p values (DV2 - logistic regression)**
Diabetes in pregnancy (gestational diabetes **OR** pre-existing diabetes) **n = 168**					
Yes	41	24 (58.5%) [42.8%, 66.2%]	p = 0.905	16 (39.0%) [23.4%, 54.6%]	p = 0.746
No	127	73 (57.5%) [48.8%, 66.2%]		46 (36.2%) [27.7%, 44.7%]	
Anaemia before AND during pregnancy n = 221					
Yes	72	53 (73.6%) [63.2%, 84.0%]	p = 0.004*	35 (48.6%) [36.8%, 60.4%]	p = 0.019*
No	149	79 (53.0%) [44.9%, 61.1%]		48 (32.2%) [24.6%, 39.8%]	
♦**Red cell folate level insufficient** before **OR** during pregnancy **n = 61**					
Yes	46	25 (54.4%) [39.4%, 69.3%]	p = 0.405	n =<15	p = 0.358
No	n =<15	n =<15		n =<15	

Footnotes:

♦AEDC require that results relating to cells sizes of 15 or less are not provided to protect confidentiality

Categorical variables are shown as absolute and relative frequencies (percentages) with [95% confidence intervals] – mother's ethnicity, region of residence, teenage mother, SEIFA, parity, Body Mass Index, smoking in pregnancy, diabetes in pregnancy, anaemia before and during pregnancy, folate levels insufficient, *p value less than 0.05

Table 5.2 - Part B						
Characteristics of mothers	**DV1 = No n = 105**	**DV1 = Yes n = 145**	**p values (logistic regression)**	**DV2 = No n = 159**	**DV2 = Yes n = 91**	**p values (logistic regression)**
Mothers' age in years at baby's birth median (IQR) [95%CI]	24 (20.5, 29.5) [22, 25]	24 (20,31) [23,26]	p = 0.570	23 (20,29) [22,24]	26 (21,32) [23, 28.4]	p = 0.101

Footnotes:

Numerical values with a skewed distribution are shown as median and inter-quartile range (IQR) and [95%CI] – mother's age in years at birth of baby
*p value less than 0.05

Early childhood anaemia was significantly associated with developmental vulnerability for four out of five domains of early childhood development: physical health and wellbeing, social competence, language and cognitive skills (school-based), communication skills and general knowledge. Smoking in pregnancy was significantly associated with developmental vulnerability on three domains: physical health and wellbeing, social competence, communication skills and general knowledge. Anaemia of mothers before and during pregnancy was significantly associated with developmental vulnerability on two domains: physical health and wellbeing, communication skills and general knowledge (Supplementary Table 5.3).

Multivariable complete case analyses found that children who had had early childhood anaemia (OR 2.2 [95%CI 1.1, 4.3] p = 0.020) were at significantly higher risk of developmental vulnerability compared to children who had not been anaemic, as were boys compared to girls (OR 2.8 [95%CI 1.5, 5.3] p = 0.001). Characteristics of mothers significantly associated with developmental vulnerability in their children included smoking in pregnancy (OR 2.0 [95%CI 1.02, 3.9] p = 0.045) and anaemia both before and during pregnancy (OR 2.1 [95%CI 1.1, 4.1] p = 0.021). Children of Aboriginal mothers were at higher risk of developmental vulnerability (OR 2.5 [95%CI 1.3, 5.0] p = 0.009) compared to children of Torres Strait Islander mothers or both Aboriginal and Torres Strait Islander mothers. The results of analysis following multiple imputation of missing values (n = 29) for mothers who were anaemic both before and during pregnancy were consistent with the results of complete case analysis (Table 5.3).

Table 5.3

Risk factors for child (n=250) developmental vulnerability (in lower 10th percentile of AEDC assessment score) in two or more domains (DV2): multi-variable analyses - complete case analyses and analysis with imputed data.

Characteristic	Complete case analysis 1 N=221				Analysis with imputed data* N=250			
	DV2 (Yes) 83 (37.6%)	**DV2 (No) 138 (62.4%)**	**Odds-ratio (95% CI)^**	**p-values**	**DV2 (Yes) 91 (35.4%)**	**DV2 (No) 159 (63.6%)**	**Odds-ratio (95% CI)^**	**p-values**
Child anaemic when aged between 6 and 23 months				p=0.020				p=0.016
No	24 (28.9%)	72 (52.2%)	1		25 (27.5%)	82 (51.6%)	1	
Yes	59 (71.1%)	66 (47.8%)	2.2 (1.1, 4.3)		66 (72.5%)	77 (48.4%)	2.2 (1.2, 4.1)	
Mother anaemic before AND during pregnancy				p=0.021				p=0.027
No	48 (57.8%)	101 (73.2%)	1		53 (58.2%)	117 (73.6%)	1	
Yes	35 (42.2%)	37 (26.8%)	2.1 (1.1, 4.1)		38 (41.8%)	42 (26.4%)	2.1 (1.1, 4.1)	
Mother smoked during pregnancy				p=0.045				p=0.016
No	25 (30.1%)	60 (43.5%)	1		26 (28.6%)	71 (44.7%)	1	
Yes	58 (69.9%)	78 (56.5%)	2.0 (1.02, 3.9)		65 (71.4%)	88 (55.4%)	2.2 (1.2, 4.1)	

Characteristic	Complete case analysis 1 N=221				Analysis with imputed data* N=250			
	DV2 (Yes) 83 (37.6%)	DV2 (No) 138 (62.4%)	Odds-ratio (95% CI)^	p-values	DV2 (Yes) 91 (35.4%)	DV2 (No) 159 (63.6%)	Odds-ratio (95% CI)^	p-values
Sex of child								
Female	26 (31.3%)	76 (55.1%)	1	p=0.001	29 (31.9%)	89 (56.0%)	1	p=0.001
Male	57 (68.7%)	62 (44.9%)	2.8 (1.5, 5.3)		62 (68.1%)	70 (44.0%)	2.8 (1.6, 5.1)	
Ethnicity of mother								
Torres Strait Islander	24 (28.9%)	67 (48.6%)	1	p=0.009	25 (27.5%)	70 (44.0%)	1	p=0.008
Aboriginal	55 (66.3%)	59 (42.8%)	2.5 (1.3, 5.0)	p=0.990	62 (68.1%)	72 (45.3%)	2.4 (1.3, 4.7)	p=0.623
Both	4 (4.8%)	12 (8.7%)	1.0 (0.3, 3.8)		4 (4.4%)	17 (10.7%)	0.7 (0.2, 2.6)	
Age of mother at birth of child								
<= 30 years	55 (66.3%)	106 (76.8%)	1	p=0.039	62 (68.1%)	124 (78.0%)	1	p=0.041
> 30 years	28 (33.7%)	32 (23.2%)	2.1 (1.04, 4.2)		29 (31.9%)	35 (22.0%)	2.0 (1.03, 4.0)	

Footnotes

Models include all variables shown, adjusted for the confounding effect of birth method (no missing values imputed).
Imputed data are averages of 20 imputations. ^95% CI = 95% confidence interval.

5.5 Discussion

To our knowledge, this is the first study to demonstrate the association of early childhood anaemia with developmental vulnerability at school age in Australia. Children who had anaemia between age six and 23 months had more than twice the risk of developmental vulnerability at school age compared to those who had not been anaemic. Early childhood anaemia was associated with developmental vulnerability in four of the five domains of early childhood development. Anaemia of mothers also doubled the risk of developmental vulnerability of their children at school age. These findings are consistent with the persistent detrimental effects of iron deficiency on neurological development in early life.[1]

One limitation of this study is the small numbers of participants. However, the number of children with a Ferret record available (n = 1,155) is close to census population information (n = 1,147) for the remote communities where the Ferret system was used (Supplementary Table 5.4). While the proportion of children with a haemoglobin measured (74.0%) is lower than expected, this is similar (85.0% and 72.1%) to two reports from elsewhere in northern Australia.[4, 8] The proportion of children with a haemoglobin measurement for whom AEDC assessment results were available - 250/708 (35.3%) - is consistent with the triennial schedule of the AEDC. Our findings in respect of child's sex, anaemia of mothers and smoking in pregnancy concur with the findings of much larger studies in South Australia and the Northern Territory.[12, 13] Nevertheless, additional studies in similar settings would be of value to confirm - or disprove - the findings reported here in respect of early childhood anaemia.

Another limitation is the absence of information on the causes of the early childhood anaemia among these children. Iron deficiency is the usual cause of anaemia in early life.[2, 9] Two Northern Territory studies found iron deficiency was the main cause of anaemia in children there; among 74 pre-school aged children with anaemia 62 (84%) were iron deficient; among 66 school-aged anaemic children, 55 (83%) responded to iron therapy.[23, 24] Comparable studies are needed for Far North Queensland.

Our findings show a higher risk of developmental vulnerability among children of Aboriginal mothers compared to children of Torres Strait Islander mothers. This reflects different historical experiences as Aboriginal people of mainland Queensland were subject to

extensive forced removals compared to the Torres Strait.[25] Loss of access to nutrient-dense traditional food was only one of many grim consequences of this policy.[25]

In settings where the prevalence of early childhood anaemia exceeds 20% - such as Far North Queensland and elsewhere in northern Australia[7,4] - the World Health Organization recommends interventions that combine nutrition promotion with provision of multi-micronutrient preparations that include iron, for fortification of complementary food.[9,26] These interventions have been shown to be safe and effective.[26] One such intervention has been successfully piloted in six remote communities across northern Australia.[27] Improvements in haemoglobin levels resulting from such interventions protect against early childhood anaemia, and are also protective against the development deficits associated with early childhood anaemia.[28]

Interventions to prevent anaemia in early childhood will be strengthened by improved food security, and by prevention and treatment anaemia in pregnancy.[5, 29] Evaluation is essential, in particular to assess if prevention of maternal and early childhood anaemia translates into improved developmental indicators for children at school-age. [1, 28]

The Australian government is committed to Closing the Gap between Aboriginal and Torres Strait Islander peoples and other Australians.[30] Anaemia prevention and better nutrition provide an opportunity to improve early childhood development, educational attainment and contribute to Closing the Gap between Aboriginal and Torres Strait Islander people and other Australians.

5.6 References

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5.7 Supplementary Materials

Supplementary Table 5.1
Data Collections - Information sources accessed to investigate the relationship between early childhood anaemia and developmental indicators at school entry age.

Year Commenced	Data Collection
1986	**Queensland Perinatal Data Collection (PDC)**
	Information on Queensland mothers and their babies is recorded at the time of birth on the Perinatal Data Collection, which commenced in Queensland in 1986. Information is collected on all live births in Queensland and on all stillbirths of at least 20 weeks gestation and/or at least 400g in weight.[1]
2001	**Ferret**
	A centralised electronic patient information and recall system rolled out in health services in Far North Queensland from 2001 to 2006.[2,3] Ferret was used mainly by community health services in thirty three remote Aboriginal and Torres Strait Islander communities (Torres Strait (n = 21) and Cape York (n = 12)) plus five locations in the vicinity of Cairns. The Ferret system rollout was completed in 2006. [2,3] Data recorded on Ferret includes information from routine adult health checks, antenatal and child health checks. Ferret was the only system in use for this purpose during the timeframe of this research
1999	**Auslab**
	Pathology Queensland provides pathology services to all Queensland Health facilities. Pathology test results are recorded on centralised electronic systems. The Auslab system, which commenced in 1999, was in use for this purpose during the timeframe of this research. [4]

Year Commenced	Data Collection
2009	**The Australian Early Development Census (AEDC) Data Collection** Every three years, the Australian Department of Education the conducts the Australian Early Development Census. Every child commencing full time school in that year in Australia is assessed by his/her teacher for early childhood development in respect of: • Physical health and well-being • Social competence • Emotional maturity • Language and cognitive skills (school-based) • Communication and general knowledge Each child is allocated a composite score and assigned to one of three categories: on track, at risk, or vulnerable [5, 6] Criteria for categories are based on the first AEDC conducted in 2009 and applied each year subsequently. Australian Early Development Censuses have been conducted on children enrolled in their first full time year of school, in 2009, 2012, 2015 and 2018

Supplementary Table 5.1 References

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Supplementary Table 5.2
Definitions of variables used to describe characteristics of Aboriginal and Torres Strait Islander children (born between 2006 and 2010) and their mothers in Far North Queensland.

Variable	Characteristics of Mothers
Maternal age	Age of a mother in completed years at the time of the birth of her baby.[1]
Teenage mother	Mother was aged less than twenty years at the birth of her baby.[1]
Parity	As reported in the Queensland Perinatal Data Collection - number of previous pregnancies resulting in live births or stillbirths, excluding the current pregnancy.[1]
Categories of Parity	For the purpose of this analysis, parity was categorised into two categories (parity nil to 2 or parity 3 or more) based on the median values for parity (median 2 (IQR 1,4) [range 0-8].
Body Mass Index (BMI) of mother	Weight in kilograms divided by height^2 in metres.[2] Weight and height measurements are those recorded in the Perinatal Data Collection based on measured or self- reported height and self-reported weight prior to or at conception[3]

Variable	Characteristics of Mothers
Implausible weight and/or height values	Guidelines to identify implausible BMI values were not identified for mothers. Instead implausible weights and heights for mothers were identified based on information on weights and heights of participants of the National Nutrition Survey 1995.[4] In 1995, no participating girl aged 12 years or more weighed less than 35 kilograms or had a height measure less than 140cm and no participating girl/woman aged 16 years or more weighed less than 40 kilograms.[4] Among the mothers of the two present cohorts, none had body weights reported of less than 35 kilograms. Four heights of less than 140cm and nine weights of less than 40 kilograms for girls/women aged 16 years or over, were replaced with missing values. At the National Nutrition Survey 1995, 0.1% of women had a height of 180cm to 190cm and 0.2% had a body weight of 130 kilograms or more.[4] Among the mothers of the two present cohorts, eight had a height measurement between 180cm and 190cm recorded which were replaced with missing vales. Eleven mothers had weights between 130 kg and 140 kg recorded. These values were considered plausible and retained.
Implausible Body Mass Index (BMI)	For women aged 18 years, the 3rd percentile of Body Mass Index for age is 17.2 kg/m^2. [5] As 3% of the reference population have Body Mass Index less than 17.2%, the definition of implausible low value for BMI was taken to be less than 16. Ten BMI values ranging from 14 up to 16 for mothers aged 18 years and over, were changed to missing. Two mothers under the age of 18 years had BMI values between 15 and 16 which were below but close to the third percentile BMI for age and therefore considered plausible.[5]
Smoking in pregnancy	As reported in the Queensland Perinatal Data Collection – any smoking recorded before and/or after 20 weeks gestation was classified as 'smoking in pregnancy'.

	Maternal health and nutrition indicators
Body Mass Index categories: mothers aged 18 years and over	BMI was categorised for mothers aged eighteen years and older, as defined by the Australian National Health and Medical Council (BMI < 18.5 underweight, 18.5 - <25.0 healthy weight, 25.0 - < 30.0 overweight, 30 or more obese).[2]
Body Mass Index categories: mothers aged less than 18 years	For mothers less than eighteen years of age, BMI was classified into the same categories (underweight, healthy weight, overweight, obese) using the criteria for girls aged between 2 years and eighteen years developed by Cole et al. (2007). These criteria have been used for child and adolescent participants of 2011 - 2013 national health surveys in Australia - the 2011-12 Australian National Health survey and the 2012-13 Australian Aboriginal and Torres Strait Islander Health survey and are the criteria recommended for analysis of survey data in the National Health Dictionary. [6, 7 8]
Anaemia in pregnancy	Haemoglobin < 110 g/L as recorded on the Queensland Pathology Auslab electronic record system and as defined by Queensland Health clinical guidelines.[9]
Anaemia before pregnancy	Haemoglobin measurements recorded on Auslab prior to the cohort pregnancy were assumed to have been measured in a previous antenatal period. The criteria for anaemia in pregnancy were applied - haemoglobin < 110 g/L - to define anaemia before pregnancy
Anaemia both before and during pregnancy	Mother had Auslab measurements of haemoglobin below the level diagnostic of anaemia in pregnancy - haemoglobin < 110 g/L - with one measurement dated prior to the cohort pregnancy AND one measurement dated during the cohort pregnancy
Pre-existing maternal diabetes	Diabetes defined using criteria as specified by the International Association of Diabetes and Pregnancy Study Groups, and by Queensland Health: fasting glucose levels of 7 mmol/L or more and/or glycated haemoglobin (hbA1c) levels of 6.5% or more. Diabetes was considered to be 'pre-existing' if a positive test result was reported before or during cohort pregnancy. [10, 11]

	Maternal health and nutrition indicators
Maternal gestational diabetes	Among mothers without pre-existing diabetes, gestational diabetes was defined as specified by the International Association of Diabetes and Pregnancy Study Groups - glucose tolerance test results: fasting glucose of 5.1 mmol/L up to 7mmol/L or one hour glucose 10.0 mmol/L or more, or two hour glucose 8.5 mmol/L or more. [10, 11]
Diabetes in pregnancy	Mother had either pre-existing diabetes OR gestational diabetes during the cohort pregnancy
Insufficient Red Cell Folate	As defined by WHO, folate status less than optimal for women of reproductive age to prevent neural tube defects - measurement results <906 nmol/L [12,13]
	Children characteristics and health and nutrition indicators
Child's sex	As recorded on the Perinatal Data Collection
Child's birth weight	Ditto
Gestational age - weeks	Gestational age at birth in weeks as recorded on the Perinatal Data Collection
Prematurity	Gestational age at birth less than 37 weeks[14]
Low birth weight	Birth weight less than 2,500g [14, 15]
Healthy birth weight	Birth weight of 2,500g up to 4,000g [14, 15]
Macrosomia	Birth weight of 4,000g or more[15, 14]
Z-score for birth weight	Birth weight z-scores adjusted for sex and gestational age were based on the International Standards for Size at Birth for newborns with gestational age of 33 weeks or more. [16] The Intergrowth-21st Network on-line calculator was used online to calculate birth weight z-scores.[17]

	Children birth up to age 2 years
Anaemia at age 6-<12 months	Child had record of one or more haemoglobin level <105 g/L when aged 6-11 months.[18]
Anaemia at age 12-<24 months	Child had record of one or more haemoglobin level <110 g/L when aged 12-23 months. [18]
Early Childhood Anaemia	Child had haemoglobin levels indicating anaemia at least once between age six months and 23 months. Haemoglobin levels of children were measured used a HemoCue at routine child health checks
Feeding to age 4-months	Child health check records on Ferret for feeding to age four months showed: breast feeding only or infant formula only or both breast feeding and infant formula or missing value.
	Children at first year of full-time school (around age 5 years)
Australian Early Development Census (AEDC)[19]	National census of early childhood development, conducted across Australia every three years since 2009. Each child in the first year of full-time school that year is assessed by his/her teacher. Teachers are assisted by cultural consultants in these assessments where appropriate.
AEDC Domains[20]	AEDC is framed around five domains of child development: • Physical health and wellbeing • Social competence • Emotional maturity • Language and cognitive skills (school-based) • Communication skills and general knowledge

	Children at first year of full-time school (around age 5 years)
AEDC Domain centile categories and criteria	• Developmentally vulnerable - score below the tenth centile for that domain • Developmentally at risk - score 11th centile up to 25th centile for that domain • Developmentally on track - score on or above 25th centile for that domain Centile cut-offs are based on AEDC 2009 scores. The same cut-off criteria are applied for each subsequent AEDC .
AEDC Domain: Physical health and wellbeing[19]	Child's physical readiness for the school day, physical independence and gross and fine motor skills
Developmentally Vulnerable – Physical health and well being	Child's score for **Physical health and wellbeing** is below the tenth centile cut-off (as per AEDC 2009) for that domain
AEDC Domain: Social competence[19]	Children's overall social competence, responsibility and respect, approach to learning and readiness to explore new things
Developmentally Vulnerable – Social competence	Child's score for **Social competence** is below the tenth centile cut-off (as per AEDC 2009) for that domain
AEDC Domain: Emotional maturity[19]	Children's pro-social and helping behaviours and absence of anxious and fearful behaviour, aggressive behaviour and hyperactivity and inattention
Developmentally Vulnerable – Emotional maturity	Child's score for **Emotional maturity** is below the tenth centile cut-off (as per AEDC 2009) for that domain
AEDC Domain: Language and cognitive skills (school-based)[19]	Children's basic literacy, interest in literacy, numeracy and memory, advanced literacy and basic numeracy

	Children at first year of full-time school (around age 5 years)
Developmentally Vulnerable – Language and cognitive skills (school-based)	Child's score for **Language and cognitive skills (school-based)** is below the tenth centile cut-off (as per AEDC 2009) for that domain
AEDC Domain: Communication skills and general knowledge[19]	Children's communication skills and general knowledge based on broad developmental competence and skills
Developmentally Vulnerable – Communication skills and general knowledge	Child's score **Communication skills and general knowledge** is below the tenth centile cut-off (as per AEDC 2009) for that domain
Developmentally Vulnerable 1 (DV1)[19]	AEDC assessment score is below the tenth centile cut-off for one or more AEDC domains
Developmentally Vulnerable 2 (DV2)[19]	AEDC assessment score is below the tenth centile cut-off for two or more AEDC domains.

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Supplementary Table 5.3

Proportion of children with characteristic categorised as developmentally vulnerable (in lower 10th percentile of AEDC assessment score at first year of full-time school) for each of the five domains of early childhood development by anaemia and smoking status.
P-values are results of Pearson's Chi-square tests.

Developmental Vulnerability (DV) by Domain	**DV - Physical health and wellbeing**	**DV – Social competence**	**DV - Emotional maturity**	**DV - Language and cognitive skills (school-based)**	**DV -Communication skills and general knowledge**
	n = 65	**n = 81**	**n = 65**	**n = 64**	**n = 68**
Early childhood anaemia (child had anaemia between 6 and 23 months)	p = 0.047*	p = 0.018*	p = 0.151	p = 0.003*	p = 0.041*
Yes (n=143)	44 (30.8%)	55 (38.5%)	42 (29.6%)	47 (32.9%)	46 (32.2%)
No (n=107)	21 (19.6%)	26 (24.3%)	23 (21.5%)	17 (16.0%)	22 (20.6%)
Mother smoked while pregnant with this child	p = 0.033*	p = 0.009*	p = 0.201	p = 0.078	p = 0.014*
Yes (n=153)	47 (30.7%)	59 (38.6%)	44 (29.0%)	45 (29.6%)	50 (32.7%)
No (n=97)	18 (18.6%)	22 (22.7%)	21 (21.7%)	19 (19.6%)	18 (18.6%)
Mother had anaemia both before and during her pregnancy with this child	p = 0.265	p = 0.047*	p = 0.639	p = 0.052	P = 0.040*
Yes (n=72)	23 (31.9%)	31 (43.1%)	20 (27.8%)	25 (35.2%)	27 (37.5%)
No (n=149)	37 (24.8%)	44 (29.5%)	37 (24.8%)	34 (22.8%)	36 (24.2%)

Footnotes * p value < 0.05.

Supplementary Table 5.4
Early childhood anaemia more than doubles the risk of developmental vulnerability at school-age among Aboriginal and Torres Strait Islander children of remote Far North Queensland; comparisons of study participant numbers with census information.

Supplementary Table 5-4a.
Comparisons of numbers of Cape York cohort child participants with Census 2006 population figures (Australian Bureau of Statistics – Community Profile Series 2006♦).

Census 2006	**Cape York remote communities**	**2006 age 0-1year (Indigenous)**
IARE 12011	Kowanyama	22
IARE 12009	Pormpuraaw	7
IARE 12007	Aurukun	20
IARE 12005	Napranum	23
IARE 12019	Mapoon	6
IARE 12017	Lockhart River	15
IARE 12015	Hope Vale	17
IARE 12013	Wujal Wujal	10
ILOC 1202501	Coen	5
Cook Shire - SSC 36537	Laura	0
Births in 2006		125
Estimated births 2006 – 2008 (3 x 125)		**375**
Cape York cohort children with PDC record of birth and Ferret record		**380**

Footnotes

IARE - Indigenous Area; ILOC - Indigenous Location; SSC – State Suburbs; IREG – Indigenous Region

Supplementary Table 5-4b

Comparisons of numbers of 2009 and 2010 cohort child participants with Census 2011 population figures (Australian Bureau of Statistics – Community Profile Series 2011[•]).

Region	ABS community profile code	Locality	Census 2011 A&TSI <1yr
Cape York	IARE303001	Aurukun	18
Torres Region	ILOC30700302	Badu	28
Torres Region	350105781	Bamaga	27
Torres Region	ILOC30700201	Boigu	3
Cape York	ILOC30300202	Coen	8
Cape York	ILOC30300301	Cooktown	5
Torres Region	ILOC30700202	Dauan	3
Torres Region	ILOC30700501	Erub	6
Cape York	ILOC30300401	Hope Vale	18
Torres Region	ILOC30700102	Horn Island	7
Torres Region	ILOC30700401	Iama Island	8
Torres Region	ILOC30300802	Injinoo	16
Cairns & Hinterland	ILOC30801502	Jumbun	3
Cape York	IARE303005	Kowanyama	22
Torres Region	ILOC30700302	Kubin	3
Cairns & Hinterland	SSC30911	Kuranda*	17
Cape York	SSC30942	Laura**	1
Cape York	IARE303006	Lockhart River	6
Torres Region	ILOC30700303	Mabuiag	3
Cape York	ILOC30300701	Mapoon	0
Torres Region	SSC31025	Masig***	7
Torres Region	ILOC30700502	Mer	4
Cairns & Hinterland	ILOC30200301	Mossman	5

Region	ABS community profile code	Locality	Census 2011 A&TSI <1yr
Cape York	ILOC30300702	Napranum	18
Torres Region	ILOC30300803	New Mapoon	11
Cape York	IARE303009	Pormpuraaw	11
Torres Region	ILOC30700402	Poruma	0
Torres Region	ILOC30700203	Saibai	11
Torres Region	ILOC30300804	Seisa	3
Torres Region	ILOC30700304	St Pauls, Moa	7
Torres Region	ILOC30700105	TI-TRAWQ	16
Torres Region	ILOC30700503	Ugar	0
Torres Region	ILOC30300805	Umagico	6
Torres Region	ILOC30700403	Warraber	6
Cape York	ILOC30300703	Weipa	16
Cape York	ILOC30201002	Wujal Wujal	0
Cairns & Hinterland	IARE302011	Yarrabah	63
Census 2011 enumeration babies aged 0-<1yr in 2011			386
Estimated number born 2009&2010 (386 x 2)			**772**
2009 and 2010 cohort children with PDC record of birth and Ferret record			**775**

Footnotes

IARE - Indigenous Area; ILOC - Indigenous Location; SSC – State Suburbs; IREG – Indigenous Region
* derived from n = 87 aged 0-4 years
** derived from n = 3 aged 0-4 years
*** derived from n = 37 aged 0-4 years

♦**Australian Bureau of Statistics Community profiles**
http://www.abs.gov.au/websitedbs/censushome.nsf/home/communityprofiles?opendocument&navpos=230

Foreword Chapter 6 (Literature Review)

In Chapters 3, 4 and 5, I have presented the results of this research showing the high prevalence of anaemia among these mothers in pregnancy and their children in early life. Among the children, I showed the association between early childhood anaemia and developmental vulnerability at school age. As discussed in Chapter 1, prevention of early childhood anaemia is important for healthy neurodevelopment in early life.

In Chapter 6, I present a narrative literature review undertaken with the aim of identifying interventions that are effective in reducing early childhood anaemia and reducing the neurodevelopmental deficit associated with early childhood anaemia.

This chapter has been written as a publication but has not yet been submitted.

> *'Optimizing nutrition during foetal and early postnatal life is a golden opportunity to impact neurodevelopment and brain function across the lifespan.'* Georgieff et al 2017[8]

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Chapter 6 Prevention of Early Childhood Anaemia; What Works?

6.1 Introduction

Anaemia in early childhood is particularly high among Aboriginal and Torres Strait Islander children in northern Australia.[1-4] While folate deficiency, infections and genetic conditions also cause anaemia, most anaemia (>80%) among Aboriginal and Torres Strait Islander children is caused by iron deficiency.[5-7] Iron is a key nutrient for healthy development in early life; iron deficiency during critical phases of neurodevelopment may have persistent detrimental effects.[8, 9] Consistent with this as described in Chapter 5 , my study showed that Aboriginal and Torres Strait Islander children in Far North Queensland who had been anaemic at 6-23 months had increased risk of developmental vulnerability at school age (OR 2.2, p = 0.02).[10]

Pasricha et al have described the determinants of iron deficiency anaemia.[11] Among Australian Aboriginal and Torres Strait Islander people, underlying determinants include dispossession with loss of land, waters and traditional food systems.[12] Traditional Aboriginal and Torres Strait Islander food systems provided foods rich in the nutrients required to prevent anaemia; shellfish, insects, lean meat.[13,14] Small quantities of these traditional foods provide sufficient dietary iron to meet the high iron requirements of early life (Chapter 1 **Error! Reference source not found.**). In northern Australia today however, while traditional foods are still harvested and highly valued, most food is purchased from remote community stores.[15]

As elsewhere, anaemia among women and young children is associated with food insecurity and poverty, described by Pasricha et al as intermediate determinants of iron deficiency anaemia.[11, 16, 17,] Low incomes and high food costs are particular issues in remote settings where a basket of basic healthy foods can cost 35-49% more than in city supermarkets.[18, 19] More Aboriginal and Torres Strait Islander people (22%) especially those living in remote settings (31%) report food security issues, compared to other Australians (3.7%).[15, 20]

These factors contribute to poor dietary intakes that are immediate determinants of anaemia, especially in pregnancy and early life when requirements are high.[20,11]

Prevention of anaemia in early life is essential for optimal childhood development. The aim of this narrative review is to identify what interventions are effective in prevention of early childhood anaemia and the associated deficit in neurodevelopment that could be applied in Australia to prevent anaemia among Aboriginal and Torres Strait Islander children in Far North Queensland and elsewhere.

6.2 Methods

Searches were conducted to identify Australian interventions designed to address the intermediate and immediate determinants of anaemia in Aboriginal and Torres Strait Islander settings[11]; food security and availability, local food production and diet quality, including nutrient density of complementary food (Table 6.1). Articles from other settings were included where equivalent experience in remote Australia was not available. Unpublished reports on interventions in Australia were included. Searches for Australian interventions were not time limited. This international literature was limited to reviews published in English in the past ten years. Only those reports providing information on outcomes of interest (changes in dietary diversity, anaemia prevalence/incidence, neurodevelopment of children) were included.

Table 6.1
Framework for searches to identify interventions effective at prevention of early childhood anaemia in remote community settings in Australia and in other settings.

Population	Primary: Babies and young children aged 6-23 months of Australian remote Aboriginal and Torres Strait Islander communities Other: Australian Aboriginal and Torres Strait Islander communities/populations; mothers, infants and young children in resource-poor settings elsewhere
Interventions (Intermediate determinants)	Prevention of anaemia by interventions focused on: • Food security and dietary diversity • Local food production
Interventions (Immediate determinants)	• Maternal antenatal supplementation • Birthing practices – cord clamping • Flour fortification - folate • Flour fortification - iron • Healthy complementary feeding • Point of use fortification of complementary food with iron-containing multi-micronutrient preparations
Control	External control group preferred but non-controlled interventions considered in Australian settings
Outcome(s)	• Dietary diversity • Iron status of infants/children • Prevalence/incidence of early childhood anaemia • Neurodevelopment in early childhood

Breastfeeding confers particular benefits for child health and neurological development.[21] For this reason, this review assesses only those interventions that are consistent with current World Health Organization and Australian recommendations for optimal infant and young child feeding; exclusive breastfeeding to around six months of age and continued breastfeeding thereafter for twelve months or longer, complemented by nutrient rich solid foods, including iron rich foods.[22, 23]

A series of searches were conducted to identify literature relevant to the different determinants of the iron deficiency anaemia. Search terms included; Austral*, Oceanic,

Abor*, Torres, food insecurity, food security, food supply, store policy, cost, price, remote, grow, garden*, hunt*, gather*, collect*, harvest, forag*, local produc*, market garden, maternal health, food, meat, compl*, fortif*, mother, child*, infant, toddler, anaemia, anemia, haem*, heme*, hb, iron, micro*, nutr*, micronutrient, folate, folic, neural tube defects. Data collections searched included Scopus, Medline Ovid, Medline Pubmed, The Cochrane Collection, CINAHL and the Australian Indigenous Health*infonet.*

6.3 Results

Searches identified 747 reports of which 241 were selected by screening on title, including 81 duplicates. Screening on abstract was done on 160 of these reports. Twenty eight interventions and reviews were identified plus three reviews of a range of interventions. One further report was identified through a reference list. Fourteen reports described interventions in Australia and eighteen were reviews of interventions in multinational settings. In addition, five reports were identified on a range of local food production initiatives with Aboriginal and Torres Strait islander people in different settings across Australia.[24-28] While these reports provide valuable information, none included sufficient information on the outcomes so are not included here. Figure 6.1 shows the results of the search and selection process. Table 6.2 shows a summary of the 32 included reports.

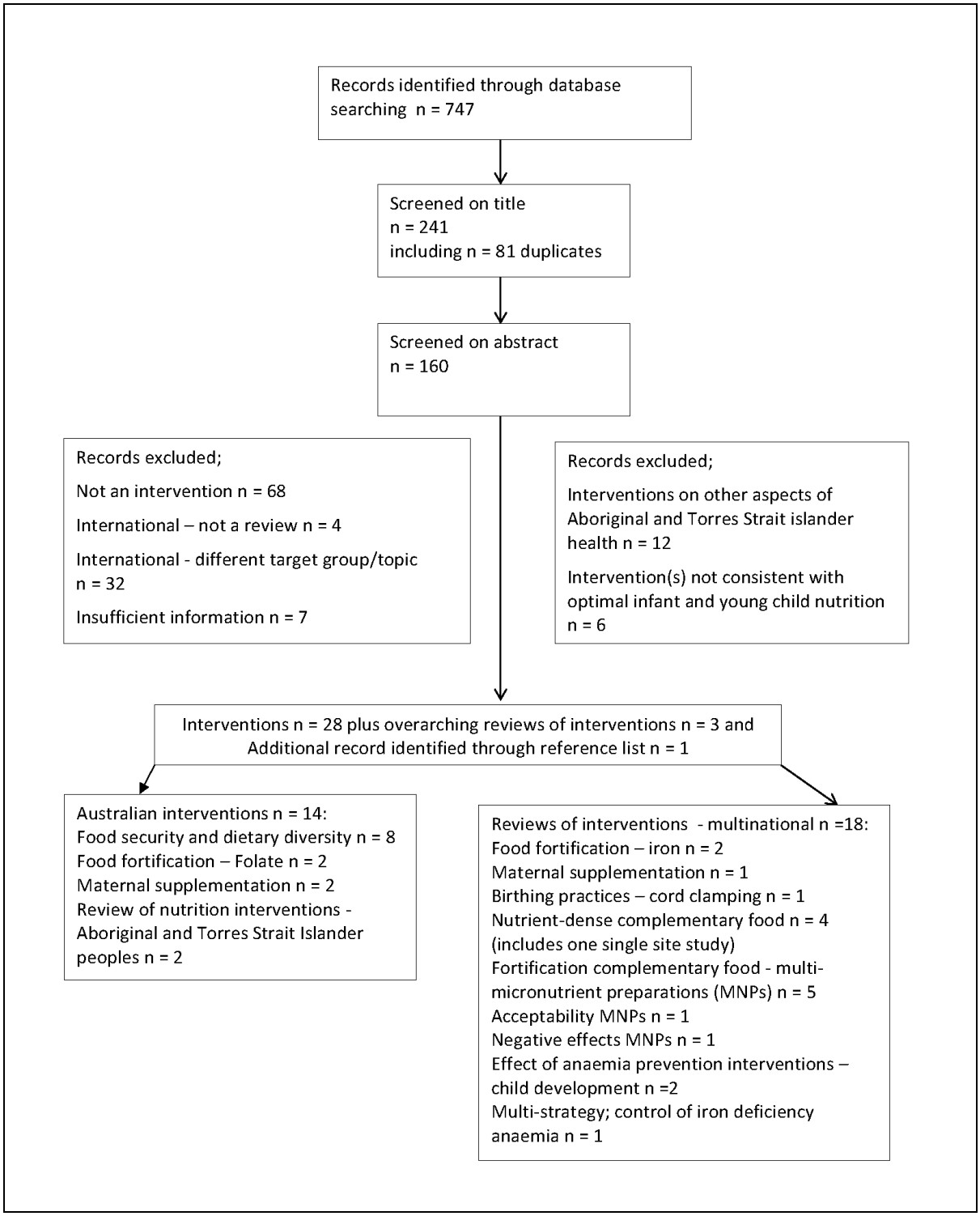

Figure 6.1 Flow diagram - review of interventions to prevent early childhood anaemia and sequelae; findings and selection results.

***Food security and dietary diversity*:** Eight reports described food security and diet diversity interventions. One report on remote community store policy initiatives spanned nearly three decades; changes over that time included increased energy content of purchases, changed purchasing patterns with less red meat and sugar sold and increased sales of convenience foods, take-away foods and sugar sweetened beverages.[19] Nutrient density, including iron density, of the purchases had declined over the 30 years. Some increases in nutrient density i.e. folate, were attributed to food fortification.[19] Other store-based interventions applied vouchers/discounts for healthy choices such as fruit, vegetables, and bottled water.[29-32] A price discount of 10% appeared to have little effect while a larger discount of 20% did achieve increases in sales of fruit, vegetable and bottled water, with effects that persisted beyond the intervention period.[29, 32] The effect of the discount activities was enhanced by promotion/educational activities.[29] Overall however, the effect of these store-based interventions was limited; generally, improvements in healthy food purchasing were small and outweighed by concurrent increases in purchasing of less nutritious choices. However, the analysis of store sales used for quantitative evaluation of store-based interventions does not support assessment of various sub-groups among customers.[30, 31] Two reports noted the potential benefits of these store-based interventions to subset(s) of community residents (those more food secure; women caring for children/grandchildren) identified by qualitative evaluations.[30, 31]

Two reports described an intervention that provided a heavily discounted box of fruit and vegetables (~90% discount) to Aboriginal families with children in rural New South Wales.[33] Despite unchanged reported intakes of fruit and vegetables during the intervention period, biomarkers of fruit and vegetable consumption showed increased intake.[33] Other outcomes reported included reduced antibiotic use, increased haemoglobin (↑1.5g/L) and reduced prevalence of anaemia (8% at baseline, 5% at follow-up).[34] The lack of an external control group however means that it is not clear if these outcomes were a result of the intervention or due to other factors such as the increased age of the children. Notably many of the child participants were iron deficient; 41% at baseline and 37% at follow-up.

A report published in 1980 described the evaluation of preschool meals and a mineral/vitamin supplement on the nutrition status of pre-school attenders aged 3-5 years compared to age/sex matched children from communities without a pre-school.[35] At

baseline 73% of attenders and 36% of non-attenders were iron deficient. Attenders showed accelerated growth rates but declines in iron status compared to non-attenders. Initial differences in iron status between the two groups were unexplained. Iron requirements are increased by rapid growth.[36] The iron content of the pre-school meals and mineral/vitamin supplement (3.6mg iron per pre-school day) may have been insufficient to meet the increased iron requirements of rapidly growing children with pre-existing poor iron status.

***Flour fortification*:** Two articles reported on the effect of mandatory fortification of bread flour with folate implemented in Australia in 2009 to prevent neural tube defects.[37,38] One reported showed that folate deficiency among Aboriginal and Torres Strait Islander people in Western Australia declined to zero, while neural tube defects were reduced by 68%.[37] The second report described a similar decline in folate deficiency in remote and non-remote areas of North and Far North Queensland, and among both Aboriginal and Torres Strait Islander people and non-Indigenous people.[38] These reports did not assess the impact of folate fortification on anaemia prevalence. Two reviews assessed the effect of iron fortification of flour (wheat or other) on haemoglobin levels and anaemia prevalence among people in various settings.[39,40] One review identified improvements in iron status of women of reproductive age but not among other groups.[40] The second review concluded that fortification with more bioavailable forms of iron had some statistically significant benefits in respect of iron status albeit small; this review recommended that fortification of flour with bioavailable iron be considered among a mix of strategies to reduce iron deficiency and anaemia.[39]

***Maternal micronutrient supplementation*:** Two reports described an Australian randomised control trial (RCT) to assess a low dose antenatal supplement among women who were non-anaemic in early pregnancy. The low dose supplement reduced iron deficiency and anaemia in pregnancy compared to a placebo with nil iron.[41] Among the children born to these mothers, 5.3% were iron deficient at age 6 months with no difference found between children of mothers who had had the iron-containing supplement compared to children of mothers who had had the placebo.[42] Current international literature on iron supplements in pregnancy focus on the optimal composition of such supplements (iron or iron/folate v multi-micronutrients).[43] No international reviews were found that assessed the effect of antenatal iron supplements on the subsequent iron status of the child.

***Birthing practice – timing of umbilical cord clamping*:** One review assessed the effect of timing of clamping of the umbilical cord on mothers and their babies.[44] This review identified that delayed cord clamping did not increase the risk of post-partum haemorrhage or retained placenta among mothers but did result in improved iron status of the baby at age 3-6 months, albeit with a small increased risk of neonatal jaundice, requiring photo-therapy.[44]

***Complementary feeding interventions*:** Four reports focused on a range of interventions to improve complementary feeding. The effect of food provision for disadvantaged children aged from 3 months to five years was reported in one review.[45] The interventions assessed, reported between 1973 and 2014, varied in provision of food, settings and outcomes reported. The authors concluded that provision of food led to gains in child weight, height, haemoglobin levels and psychomotor development but found no evidence of benefit in terms of mental development.[45] Another review assessed interventions using an RCT design that provided education about complementary feeding practices.[46] The authors found that education alone did change behaviour in respect of timing of introduction of complementary food, nutritional quality of complementary food and hygiene practices. Some benefit was reported in psychomotor development. No effect was seen in respect of child growth. Effects on child haemoglobin and/or anaemia were not reported.[46]

One review assessed interventions to increase the nutrient density of complementary food by including inclusion of meat in complementary food.[47] These studies were conducted in high resource settings and overall the inclusion of meat provided no significant benefit compared to fortified food but reported that meat as a complementary food may be beneficial to breastfed babies.[47] One study was included that compared meat (~0.27 mg iron per day) or iron-fortified cereal (1.1mg iron per day) with local unfortified cereal (0.04 mg iron per day) as complementary food for breastfed babies and young children aged 6-23 months (n = 1,298) in a poor region of China.[48] This international report is not a review but is included here as the only example identified of an intervention using meat as a complementary food in a low-resource setting. Both interventions improved iron status compared to local cereal; the effect of fortified grain on iron status was greater than the effect of meat but was associated with higher levels of inflammation.[48]

Multi-micronutrient preparations (MNPs) for fortification of complementary food for infants and young children: Five reports examined the effect of point-of-use fortification of complementary food for young children with multi-micronutrient preparations (MNPs). These are preparations, usually as powder in single-dose sachets, designed to be added at 'point-of-use' to complementary food for babies and young children from age 6-23 months.[49] Minimum recommended dosage and duration is one sachet on 90 days out of any 6 month period.[50] MNPs increase nutrient density of complementary food, without alerting taste or increasing the volume of the food; one dose provides approximately the recommended daily dietary intake amount of iron (~10mg), vitamin A, zinc and other vitamins and minerals.[51] The iron content of these preparations is encapsulated to prevent nutrient-nutrient interactions and possible unpleasant organoleptic effects of added iron.[49, 51] Lipid-based multi-micronutrient preparations provide energy and essential fatty acids as well as the minerals and vitamins found in multi-micronutrient powders.[52] WHO recommends the use of MNPs incorporated into programs to promote optimal infant and young child nutrition in settings where anaemia prevalence at age 6-23 months exceeds 20%.[53] Such interventions are currently used in more than fifty countries.[49]

One report described a feasibility trial of such an intervention to prevent early childhood anaemia in six remote Aboriginal and Torres Strait Islander communities in northern Australia; this intervention incorporated nutrition promotion with provision of a multi-micronutrient preparation (Sprinkles Plus®).[54] This is not a peer reviewed report but is included here as the only example identified where such an intervention has been trialled in Australia. Key findings were the unexpected high prevalence of anaemia (44%) among participating children aged 6-23 months (n = 262) at recruitment; anaemia prevalence was higher (56%) at age 6-8 months.[54] Among those children who were non-anaemic when recruited (n = 31) and had at least 60 single-dose multi-micronutrient sachets delivered, haemoglobin levels were maintained. Among non-anaemic children (n = 51) who received less than 60 doses, haemoglobin levels dropped but the difference between these groups was not statistically significant (p = 0.09).[54]

Four reviews assessed multi-micronutrient fortification of complementary food in settings outside Australia.[55, 56,52, 57] One review assessed both trials to prevent, and trials to treat early childhood anaemia in low- and middle-income countries.[56] For prevention, multi-

micronutrient fortification of complementary food reduced anaemia prevalence by between 30% and 50%; for treatment multi-micronutrient fortification was as effective as iron drops, more acceptable to families and safer. [56] This review recommended that multi-micronutrient fortification should not be offered in isolation but embedded in programs promoting optimal infant and young child feeding.[56] The review also identified areas that require further research such as optimal formulation, duration and frequency, and environmentally-friendly packaging.[56] A subsequent review assessing the effectiveness of home fortification of complementary food with multi-micronutrient powders in prevention of early childhood anaemia reported an overall reduction in anaemia prevalence by 31% and in the prevalence of iron-deficiency of 51% in children under age two years.[55] A similar finding was reported by a review which assessed the effectiveness of fortification of complementary food or solid food using micronutrient powders for children aged from age 6 months in developing country settings; incidence of anaemia was reduced by 34%, iron deficiency by 57% and haemoglobin levels were increased.[57] No effect was found on growth parameters but this review identified a small but significant increase in the incidence of diarrhoea.[57]

One of these four reviews compared lipid-based multi-micronutrient preparations with multi-micronutrient powders.[52] Lipid-based multi-micronutrient preparations were effective in improving child growth, reducing wasting, stunting and underweight of children; anaemia prevalence was also reduced albeit to a lesser extent (21%).[52]

One review assessed acceptability of multi-micronutrient preparations and adherence to the recommended frequency of use.[58] Adherence in most interventions (n = 17) was over 80%. Families and carers found the product acceptable.[58] Minor gastrointestinal side-effects were reported, mostly associated with initial use of the preparations.[58] Related to this, another review assessed the evidence for negative effects of MNPs on child health due to alterations in gut microbiome as a result of unabsorbed iron.[59] This review suggested alterations to the composition of MNPs such as inclusion of more bioavailable forms of iron at lower levels, with probiotics to support healthy gut microbiome.[59]

***Effect of anaemia prevention on child development*:** Two reviews were identified that assessed the effect of anaemia prevention interventions on early childhood development. The first of these found clear evidence of benefit in cognitive performance in providing iron supplements to school aged children but a lack of equivalent evidence for interventions in pregnancy and in early childhood.[60] A subsequent review assessed the effects of increased haemoglobin on child growth, development and disease in children under five years of age.[61] This review reported significant associations between effects on haemoglobin levels and benefits in motor and mental development.[61] The association was strongest among children with lower initial haemoglobin levels.[61] However benefits were also seen in children with higher haemoglobin levels, including non-anaemic children with haemoglobin levels >110g/L.[61] The authors concluded that those interventions that have a larger effect on haemoglobin levels tend to have larger effect on motor and mental development.[61] The authors attributed these findings to possible increased energy supply to the developing brain resultant from higher levels of haemoglobin; increased activity and social interaction; increased supply of iron and other nutrients required for specific neurodevelopmental processes.

***Food and nutrition interventions*:** Two Australian reviews described public health nutrition interventions designed to improve nutrition and health of Aboriginal and Torres Strait Islander Australians. One review assessed a range of interventions including the food security and dietary diversity studies described above[19, 29, 31, 32, 34, 35]; other studies included in this review focused on promotion of healthy eating, healthy weight and prevention of chronic disease.[62] Two of the twenty six studies reported assessed iron status and haemoglobin among child participants.[34, 35] The second review was a systematic review of reviews of food and nutrition interventions for Aboriginal and Torres Strait Islander Australians that examined what interventions are effective and why.[63] Effective food and nutrition programs included integration of nutrition and breastfeeding education into 'Mother and Baby' programs, and community based nutrition education and advice for parents and carers.[63] Features listed to harness community strengths for program success emphasised community direction and control, a welcoming, culturally safe environment, effective communication and feedback, and valuing and supporting Aboriginal and Torres Strait Islander staff.[63] The review also flagged provision of food to children who are food

insecure as a potentially effective intervention used overseas that could also be effective in the Australian context.[63]

Control of iron deficiency anaemia: One review assessed a range of strategies to prevent iron deficiency anaemia.[11] The fundamental causes of anaemia - poverty and food insecurity – need to be addressed.[11] Interventions identified to effectively prevent anaemia that could be implemented in the short term included multi-micronutrient fortification of complementary food for infants and young children and iron-containing supplements for mothers in pregnancy. Medium term interventions include food fortification and bio-fortification.[11] Programs to control iron deficiency anaemia should incorporate a range of strategies; short, medium and long term.[11]

Table 6.2
Summary of interventions addressing prevention of early childhood anaemia and/or factors contributing to early childhood anaemia.

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
1. Intermediate determinants: Food security and dietary diversity	Lee et al 2015 [19]	1986-2014 remote community stores - central Australia n = 5-7	Store policy to support stocking and sales of healthy choices	Longitudinal mixed methods study, pre/post comparisons food and beverage sales, nil statistical analysis	Increased availability and sales of healthy choices outweighed by increased availability and sales of nutritionally poor choices. Decline in red meat sales and iron density, increased density some nutrients eg folate due food fortification not improved dietary patterns	No	Apparent decline over time in dietary quality despite effectiveness of store policy in increased availability and accessibility of healthy choices. **Conclusion:** Intervention unlikely to reduce early childhood anaemia

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
2. Intermediate determinants: Food security and dietary diversity	Ferguson et al 2017[32]	2009 – 2011 Remote community stores in northern Australia n = 18	Price discount 10% some grocery, fresh fruit, vegetables, diet drinks	Sequential mixed methods including pre/post total sales and sales of discounted products	Nil changes in sales. Qualitative evaluation provided information for future initiatives	No	Discount insufficient to achieve changes in purchasing. **Conclusion:** Intervention unlikely to reduce early childhood anaemia
3. Intermediate determinants: Food security and dietary diversity	Brimblecombe et al 2017[29]	Mid 2012 – 201, remote community stores in northern Australia n = 20	20% discount on fruit, vegetables and diet drinks for 24 weeks in each store (promotional activities implementation incomplete)	Step-wedged Randomised Control Trial (RCT)	Small but significant increases in sales of fruit and vegetables (12g/day increase = 12.7% combined fruit and vegetables p = 0.0031); further increase post-intervention (19.8% p = 0.0033)	No	Larger discount resulted in purchasing changes, larger discount may result in further increases **Conclusion:** Intervention unlikely to reduce early childhood anaemia

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
4. Intermediate determinants: Food security and dietary diversity	Brimblecombe et al 2018[30]	Mid 2012 – 201, remote community stores in northern Australia n = 20	Assessment mediators and moderators of above intervention	Qualitative evaluation pre-, end and 24 weeks post intervention	Increased vegetable consumption during intervention reported by small number of community members who had higher self-efficacy and more food security than others	No	Diverse interventions effects on sub-groups in community may not be identified by quantitative evaluation methodology used **Conclusion:** Intervention unlikely to reduce early childhood anaemia
5. Intermediate determinants: Food security and dietary diversity	Brown et al 2019[31]	2015, remote community northern Australia n = 1	Discount vouchers for purchase of additional fruit and vegetable provided to customers already purchasing set amount – duration 32 weeks	Mixed methods feasibility trial, pre/post sales	Nil change fruit and vegetable sales; qualitative intervention suggests possible intervention benefits for sub-group (carers small children)	No	Diverse interventions effects on sub-groups in community may not be identified by quantitative evaluation methodology used **Conclusion:** Intervention unlikely to reduce early childhood anaemia

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
6. Intermediate determinants: Food security and dietary diversity 7. As above	Black et al 2013a[33] Black et al 2013b[34]	from 2005, rural Australia, Aboriginal families n = 55, 3 localities, children age 0-17 years n = 174; on follow-up n = 143	Weekly box fruit and vegetables per family discounted by ~90% of actual cost for 12 months	Longitudinal, pre/post evaluation	Nil change self-reported fruit and vegetables intakes but increase in haematological measures of fruit and vegetables intakes (n = 115, carotenes, vitamin C, p <0.05) antibiotic prescribing reduced (p<0.05), nil change anthropometry	Yes Increase in mean haemoglobin (1.5g/L increase, p < 0.05) Prevalence anaemia unchanged (8% at baseline, 5% at follow-up, ns) Prevalence iron deficiency unchanged (41% at baseline, 37% at follow-up, ns)	Substantial subsidy improved diet diversity Notable high prevalence of iron deficiency among these children Intervention achieved small improvements in haemoglobin levels; nil external controls so not clear due to intervention **Conclusion:** Intervention unlikely to reduce early childhood anaemia

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
8. Intermediate determinants: Food security and dietary diversity	Coyne 1980[35]	1997-78 Aboriginal children n = 190 age 3-5 years; n = 116 on follow-up Intervention rural (4) and urban (1) settings with pre-school plus 5 matching control settings without preschool	Nutritious meals/snacks plus vitamin/mineral supplement containing iron (3.6 mg) for pre-school children v age/sex matched controls in similar communities without preschool	Longitudinal evaluation of nutritious school meals plus mineral/vitamin supplement	Increased rates of growth in preschool attenders v non-attenders; significant decline in ferritin and haemoglobin levels among pre-school attenders v non-attenders	Yes Baseline 73% pre-school attenders iron deficient v 36% non-attenders Post intervention; pre-school attenders mean ferritin 15.4ug/L (SD 6.8) v non-attenders 24.1Ug/L (SD16.5) p<0.05; preschool attenders mean haemoglobin 116.8 mg/L (SD8) v non-attenders 126 g/L (SD16.5) ns	Decline of ferritin levels may reflect increased requirements due to accelerated growth. Difference in baseline iron status unexplained – may reflect different nutrient density of diet of non-attenders eg traditional foods **Conclusion.** Interventions to increase child growth rate can have negative effect on iron status

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
9. Intermediate determinant – fortification	Bower et al 2016[37]	2008 - 2014 (dietary intake); 1980 - 2014 (neural tube defects) Aboriginal and Torres Strait Islander people n = 95; resident in regional and metropolitan Western Australia	Mandatory fortification of bread flour with folate from September 2009	Pre and post-intervention comparisons; diet intake, haematological measures, incidence neural tube defects (NTD) compared with information from similar studies pre-fortification	Mean red cell folate levels increased in men and women p <0.0001; folate deficiency reduced pre-fortification 10% in women and 26% in men to post-fortification zero. Other sources of folate from diet/supplements were unchanged compared to pre-fortification. NTDs among Aboriginal and Torres Strait Islander people reduced 68%. Nil evidence vitamin B12 deficiency.	No	Folate fortification highly effective in improving folate status and reducing NTDS in this metropolitan/regional Aboriginal and Torres Strait Islander population **Conclusion:** Intervention may have achieved reduction in anaemia due to folate deficiency

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
10. Intermediate determinant – fortification	Slagman et al 2019[38]	2004 – 2015 Population of northern Queensland including Aboriginal and Torres Strait Islander people who had routine measurements of red cell folate (n = 14,792 measurements)	Mandatory fortification of bread flour with folate from September 2009	Pre and post-intervention comparison of routinely collected health service measurements of red cell folate from before and after mandatory fortification of bread flour with folate	Prevalence of folate deficiency among Aboriginal and Torres Strait Islander people reduced by 93% from 17.4% to 1.3%, p<0.001.	No	Folate fortification highly effective in improving folate status Aboriginal and Torres Strait Islander people in northern Queensland **Conclusion:** Intervention may have achieved reduction in anaemia due to folate deficiency
11. Intermediate determinant – fortification	Pachon et al 2015[40]	2004-2013 Women of reproductive age, adolescent girls, school children, pre-school-age children n = 19,410	Fortification of flour (wheat or maize) with iron. All interventions commenced prior to WHO 2009 recommendations on fortification – only two used iron amount and type consistent with	Systematic review; 13 studies	Consistent reduction in low ferritin among women. Mixed results for changes for haemoglobin levels and anaemia prevalence in women and in	Yes; haematological indicators reported varied by study – ferritin levels, haemoglobin levels , anaemia prevalence	**Conclusion:** if current recommendations for iron fortification of flour are followed, this may improve iron status of women. Unlikely to reduce early childhood anaemia due to small

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
			current recommendations		children. Improved study design needed to assess implementation		quantities solid food eaten.
12. Intermediate determinant – fortification	Sadighi et al 2019[39]	1963-2016 High, middle and low income countries mean duration 20.6 months; includes one study in remote Australian remote Aboriginal and Torres Strait Islander community (Kamien 1975). Various participants; women of reproductive age and/or	Evaluation of fortification of wheat flour and/or other flours (maize, rye, soy, rice) and/or food products eg biscuits made with fortified flour	Systematic review and meta-analysis of RCTs (n = 49) pre/post trials n = 45	RCT trials higher quality - meta-analysis RCTs showed; mean haemoglobin levels increased (2.63 g/L p <0.001); mean serum ferritin increased (8.544ug/L p <001) anaemia reduced 8.1% p <0.01).	Yes	Iron fortification of flour is effective but the effect small; useful to include in a mix of strategies to prevent anaemia if the more bioavailable forms of iron (eg NaFeEDTA) used. - possible negative effects of iron fortification not considered in this review **Conclusion:** Intervention may contribute to reduced early childhood anaemia

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
		pregnant women, infants >age 6 months, pre-school children, school-aged children, adolescents, lactating mothers, all population					
13. Intermediate determinant – antenatal supplements	Makrides et al 2003[41]	1997-99, Australia urban setting, non-anaemic pregnant mothers, average age 28 years n = 430, n = 366 on follow-up	Daily low dose iron (20mg per day) antenatal supplements v placebo without iron from 20 weeks gestation	RCT	At delivery, iron supplement 35% iron deficient v placebo 58% iron deficient p<0.005, supplement 3% iron deficient anaemia v placebo 11% p <0.001. Postpartum 6 months, supplement 16% iron deficient v 29% p = <0.005,	Yes	Low dose iron supplementation in pregnancy effective in improving iron status during and after pregnancy and reducing anaemia during pregnancy

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
					nil difference in anaemia		
14. Intermediate determinant – antenatal supplements	Zhou et all 2007[42]	1197 – 99 At age 6 months, babies of mothers in above trial, Australia urban setting	Mothers had low dose iron antenatal supplements v placebo without iron during pregnancy	RCT	Nil differences in haemoglobin levels, iron status or anaemia at age 6 months between babies of supplemented mothers v placebo group mothers	?	Overall 5.2% of babies were iron deficient at age 6 months, nil had iron deficiency anaemia **Conclusion:** Intervention unlikely to alter risk of anaemia among babies of well-nourished mothers; effect may be different where mothers less well-nourished
15. Intermediate determinant – antenatal supplements	Keats et al 2019[43]	2003- 2014 low/middle income (19), high income country (1) (not Australia), 141,849 women	Comparison of different forms of antenatal supplements on pregnancy outcomes Multi-micronutrient (MMN)	Cochrane review	MMN supplements small reduction in relative risk of baby small for gestational age p = 0.00038, low birth weight p<0.00001, nil difference	Yes, of mothers	Not reported if multi-micronutrient formulation of iron containing antenatal supplements provide additional benefits in reducing early childhood anaemia

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
			supplementation in pregnancy v other (iron only OR iron and folate) supplements		neonatal mortality, maternal anaemia third trimester, maternal mortality v iron folate/iron only		**Conclusion:** benefits in respect of early childhood anaemia not clear
16. Immediate determinants – timing of umbilical cord clamping	McDonald et al, 2013[44]	1996-2012, high income x 7 (including Australia), low/middle income countries x 6, 2 not stated; 15 trials, 3911 mother and child pairs where baby was full term - three trials included caesarean births	Late clamping of umbilical cord v early clamping; early = less than 1 minute after birth	Cochrane Review	Late v early clamping did not increase risk of maternal postpartum haemorrhage p = 0.88 Late v early clamping increase neonatal jaundice p = 0.032	yes Early clamping v late increased risk of infant iron deficiency at age 3-6 months p =0.041	Early cord clamping effectively results in blood loss by infant. **Conclusion:** Delayed cord clamping is effective in improving infant iron status so would reduce early childhood anaemia

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
17. Immediate determinants – nutrient dense complementary food	Kristjansson et al 2015[45]	1973-2014, low and middle income countries (29), high income (3) socially disadvantaged children age 3 months up to five years (n = 30 up to n = 3,166) (including n = 116 remote community Aboriginal children in Australia; Coyne 1980)	Various supplementary food (<15% to >50% energy requirements, with or without added micro-nutrients), duration 3 to 32 months, mean 10 months, median 9 months 5 RCTs – intervention was provision of micronutrient fortified foods	Cochrane Review	Primary outcomes growth and psychosocial development; for 5 RCTs outcomes included changed in haemoglobin levels	Yes, 5 RCTs of micronutrient fortified foods intervention; increased haemoglobin levels by 0.5 SD p = 0.021 (n = 300 children)	**Conclusion:** provision of micronutrient fortified supplementary food may contribute to improved haemoglobin and reduced anaemia among socially disadvantaged children
18. Immediate determinants – nutrient dense complementary food	Arikpo et al 2018[46]	2005 - 2017 high (5 studies including 3 in Australia) middle (14	Educational interventions to improve complementary feeding practices;	Cochrane review	interventions were effective in improving complementary feeding practices;	No; focus of review was on changes to breastfeeding and complementary feeding practices,	**Conclusion:** education may improve infant and young child nutrition; benefits in respect of

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
		studies) and low (3) income countries plus one setting unclear, n = 11,170 children from birth - 24 months	duration exclusive breastfeeding, age at introduction, type and amount complementary food hygiene - provision of various supplements in some interventions		effects on child growth; haemoglobin and anaemia prevention varied	not haematological indicators	anaemia prevention not known
19. Immediate determinants – meat based complementary food	Obbagy et al 2019[47]	1995 – 2013 14 x High income countries, 1 x middle/low income (two studies in Australia, Makrides 1998, 2002) 15 studies; age ranges various; from age 4 to 20 months – breastfed and/or formula	Various; meat-based complementary food compared with iron or iron/zinc fortified cereal, high meat intake v low meat intake, meat-based complementary food v 'toddler' fortified milk	Systematic review	Overall no difference between intervention and control groups where control had iron fortified food(s). Benefits of either meat or iron fortified foods strongest in breastfed babies/young children and in	Yes Various; significant difference between meat/fortified foods v non-fortified control (4 studies)	**Conclusion:** Food fortification appears equally effective as consumption of meat-based complementary foods in maintaining iron status and prevention of anaemia among vulnerable children

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
		fed and/or fortified milk			those with poor iron status		
20. Immediate determinants – meat based complementary food	Ma et al 2016[48] Note: single study only, not a review – included here as an example of an intervention with meat as a complementary food in a low income setting	2009 -2011 China (Xichou county, Yunan Province; 1400 masl) children aged 6-24 months, Infants/young children age 6 – 18 months; n = 1465 n = 1298 completed study	Two interventions plus control group ; Families given 50g raw pork per day (iron content not stated- 50g Australian raw pork provides 0.27mg iron - AusNut 08A30403) to cook & feed to child (MG) OR 50g fortified rice cereal – 1.1 mg iron per day (FG) OR 50g non-fortified rice cereal – 0.04 mg iron per day (LG)	Cluster randomised RCT	Iron deficiency lowered by FG more than by meat and by both FG and meat more than LG Nil difference in haemoglobin levels between the three groups Note: meat is a highly desirable food in a low resource setting; leakage may have occurred – nil information	Yes Hameoglobin g/L (122.3 (MG); 121.6(FG) 119.5 (LG) ns p = 0.150) Serum Ferritin ug/L (17.7 (MG); 18.95 (FG); 15.2 p = 0.043) Iron deficiency % (42% MG); 32% (FG); 53% (LG) p = 0.010 Anaemia% (11 (MG); 10 (FG) 22 (LG) p = 0.021)	Fortified grain and meat improved iron status and reduced anaemia more than local grain; fortified grain greater effect than meat but also more systemic inflammation **Conclusion:** Both interventions (meat and fortified grain) effective in reducing early childhood anaemia

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
						Systemic inflammation % (18.3 (MG); 31 (FG) 22 (LG) p = 0.042	
21. Immediate determinants - Micronutrient fortification of complementary food	Dewey et al 2009[56]	**Prevention of anaemia:** 2003-2007 children aged 6 – 36 months n = 4,752; high income x 1 (Canada), low/middle income countries x 10 (nil studies in Australia) **Treatment of anaemia:** 2001-07 children aged 2 – 24 months n = 1,361;	Prevention MMN fortification of complementary food v usual feeding Treatment MNPs v MNPs at different iron doses 12.5, 20, 30mg v iron drops	Systematic review and meta-analysis	MNPs effective in prevention of anaemia Effect of treatment – ns difference MNPs and iron drops	Yes **Prevention:** effect size ferritin levels +0.36, p = 0.004; haemoglobin levels +5.1g/L p =0.008; RR anaemia 0.54 **Treatment:** RR anaemia MMN v iron drops 1.04 ns difference	MNPs safe and acceptable to families; MNPs best embedded in promotion of optimal infant and young child nutrition **Conclusion:** MNPs with nutrition promotion effective in preventing and treating early childhood anaemia

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
		low/middle income countries x 5 (nil studies in Australia)					
22. Immediate determinants - Micronutrient fortification of complementary food	Salam et al 2013[57]	2006-2012 low/middle income countries (nil studies in Australia) 17 trials n = 17,305; most participants under age 6 years, two trials included children up to 11 years old	MMN fortification of children's food v usual food Researchers were unable to identify research reporting on benefits of MNPs for women	Systematic review and meta-analysis	MNPs reduced prevalence of anaemia by 34% and improved haemoglobin levels Also increased diarrhoea mainly in one study. Nil effect on growth, may be due to increased diarrhoea	Yes MNPs RR anaemia 0.66 p <0.0001, Std mean difference haemoglobin +0.98 p < 0.0001	Planning for interventions using MNPs should consider risk of increased diarrhoea **Conclusion:** MNPs effective in preventing and treating early childhood anaemia but may be increased diarrhoea

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
23. Immediate determinants - Micronutrient fortification of complementary food	Aquino et al 2013[54] Note: report - not peer reviewed publication	2010-2012 Remote communities across northern Australia n = 6; children birth to age 2 years n = 262	Nutrition promotion combined with provision of multi-micronutrient powder (MMN)for fortification of children's complementary food	Feasibility trial	Intervention acceptable to families; unexpected high prevalence of early onset anaemia and logistical challenges in some settings compromised implementation	Yes Among non-anaemic children at recruitment (n = 82) mean baseline haemoglobin = 115 mg/L; children n = 13 sufficient MNP supply haemoglobin levels stayed constant v children n = 51, insufficient supply mean haemoglobin declined to 107g/L note - difference not significant p = 0.09	**Conclusion:** Nutrition promotion incorporating MNPs is feasible in remote Australian settings and may be effective in prevention of early childhood anaemia remote Australian setting. Given the high prevalence of early childhood anaemia in this setting, MNPs may have additional value for treatment as well as prevention
24. Immediate determinants - Micronutrient fortification of	De-Regil et al 2014[55]	2001-2011 low income countries	MMN fortification v placebo fortification v usual food	Cochrane review	In children under 24 months, MNPs reduced anaemia by 31%, iron	Yes Anaemia RR 0.69; iron deficiency RR	**Conclusion:** MNPs effective in preventing and treating early childhood anaemia

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
complementary food		(nil studies in Australia) 8 trials; children age 6-36 months n = 3,748			deficiency by 51%, nil effect on growth	0.49; haemoglobin g/L +5.87 p<0.001	
25. Immediate determinants - Micronutrient fortification of complementary food	Das et al 2019[52]	2007 - 2018 Low and middle income countries (nil studies in Australia) n = 23,200 age 6-23 months	Lipid-based Nutrient Supplements (LNSs) v Fortified Blended Food (FBF) OR MNPs (LNSs provide energy + essential fatty acids = micronutrients)	Cochrane review	LNS v nil intervention; growth parameters improved; anaemia reduced	Yes Anaemia RR 0.79	LNS supporting growth – useful to prevent stunting/wasting **Conclusion:** LNSs effective in preventing early childhood anaemia but effect less than MNPs
26. Immediate determinants - Micronutrient fortification of complementary food	De Barros 2016[58]	2005 – 2013 High (USA and Canada), low and middle income countries (nil	Assessed adherence to, and acceptability of MNPs (powders in single dose sachets)	Systematic review	Adherence ranged from 50% to 90% prescribed quantity; MNPs well received due caretaker	No	**Conclusion:** MNPs acceptable to families despite some side-effects

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
		studies in Australia) 17 studies, children aged 6-23 months n = 10,651			perception of benefits to children's health, easy of transport/use , lack of effect on taste of children's food; BUT some reported food taste changes and 3-32% side-effects included diarrhoea, vomiting, constipation		
27. Immediate determinants - Micronutrient fortification of complementary food	Paganini, Zimmermann 2017[59]	2002-2017 Low, middle high income countries 17 RCTs (nil studies in Australia)	Review of evidence for negative effects of iron fortification/supplementation on gut microbiome of infants and children and increase diarrhoea morbidity	Review	MNPs containing high doses of poorly absorbed iron can alter gut microbiome increasing risk of diarrhoea; risk varies with setting and is lower where	No	Lower iron content (5mg iron /day; 2.5 mg Ferrous fumerate plus 2.5mg NaFeEDTA) appears effective against anaemia without increasing diarrhoea. Inclusion of probiotic oligosaccharides could

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
					sanitation and hygiene are better.		further protect microbiome
28. Iron supplementation antenatal and post-natal; effect on neurological outcomes of children	Larson et al 2017[60]	1986 – 2014 antenatal interventions x 4 (1 in Australia); pre-school-aged interventions x 17, school-aged intervention x 9; high x5, low/middle income countries x 13; review x 1 iron supplementation in school-aged children n = 5,143	Iron containing supplements , v iron containing supplements (x 1 trial) OR nil-iron-placebo (x 1 trial) with other micronutrients for pregnant mothers Iron containing supplements for children v nil-iron-placebo	Review	Antenatal; no difference in cognitive score of children assessed at school age (6-9 years) x 2 OR in infancy x 2. Pre-school age; Cognitive development improved in anaemic children and iron deficient children receiving parenteral iron in 8 days – no benefit for non-iron-deficient children. Other iron	Not reported in this review	Interventions varied in dosage/duration/trial populations – effect of intervention(s) on haemoglobin not described. Parenteral delivery of iron had demonstrated benefit for poor iron status children Difficult to assess development at younger ages **Conclusion:** clear benefits of iron supplementation for school-aged children

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
		(nil post-natal interventions in Australia)			supplementation interventions did not show benefit among pre-school children. Anaemic school-aged children showed cognitive benefits.		who are anaemic but not clear if pre-school aged children will benefit
29. Prevention iron deficiency/early childhood anaemia; effect on neurological outcomes	Larson et al 2019[61]	up to 2018 56 intervention trials; high x 7 (USA x2, Canada, Canada, Greece, Sweden, UK) low/middle income counties x 49 (nil studies in Australia)	Supplementation/fortification with iron with or without other micronutrients; children under 5 years n = 15,882 (including some children aged 60-72m)	Systematic review and meta-analysis	Increases in haemoglobin levels resulting from iron supplementation with or without other nutrients, were significantly associated with increases in motor and mental development	Yes Association of intervention effects on haemoglobin concentration AND mental and cognitive development was significant p <0.05	**Conclusion:** In settings where iron deficiency and early childhood anaemia are prevalent, interventions that are effective in improving haemoglobin levels also result in improved neurodevelopment in early life

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
					For each 1SD increase in haemoglobin level, motor scores increased by 0.28 SD and mental scores increased by 0.24 SD		
30. Nutrition interventions (Australia)	Gwynn et al 2019[62]	1980-2017 Nutrition education and promotion programmes (n = 7) Store-based intervention with concurrent community programs (n = 5)	A review to identify which nutrition interventions work to improve diet and health-related outcomes among Australian Aboriginal and Torres Strait Islander people	Systematic review – selection protocols excluded interventions using nutrient supplements	Promising interventions are; store-based interventions with community health promotion in remote settings; fiscal strategies; nutrition education and promotion. Evaluation and scaling up required, plus	Yes *See Black et al, Coyne et al above*	**Conclusion:** Strong engagement with Aboriginal and Torres Strait Islander communities is essential for effective interventions to reduce anaemia in early childhood

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
		Return to traditional lifestyle (n = 3)			wider geographical scope. Engagement with Aboriginal and Torres Strait Islander community essential for effective programs		
31. Nutrition interventions (Australia)	Browne et al[63]	2005-2015 11 reviews included; Maternal health and parenting n = 2 Childhood health and development n = 3	A review to identify which programs are effective in improving diet and health-related outcomes among Australian Aboriginal and Torres Strait Islander people, and why	Review of systematic reviews	Effective interventions include incorporating breastfeeding and nutrition advice into maternal and child health services; community involvement – ideally community	No	**Conclusion:** Intervention(s) to reduce early childhood anaemia among Aboriginal and Torres Strait Islander children could be incorporated into maternal and child health services. Community control/design of interventions essential

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
		Adolescent and youth health n = 1 Healthy adults and healthy aging n = 5			control – in design and implementation is key factor for program success		
32. Interventions to control iron deficiency anaemia	Pasricha et al 2013[64]	2001 – 2011 (multilateral agencies guidelines for anaemia control e.g. WHO)	Review of evidence for control of iron deficiency anaemia in low and middle income countries	Review	Effective; daily or intermittent iron supplementation; food fortification; MNPs; antihelminth therapy; delayed umbilical cord clamping; ultimately - food security and poverty alleviation. Possible negative effects of iron for people who are iron replete; exposed to	No	**Conclusion:** Long term solutions require fundamental changes food security and poverty alleviation. MNPs for infants and young children, and iron supplementation for women/older children are effective solutions.

Intervention type	Reference	Timeframe, setting, participants	Intervention	Study design	Outcome	Outcome measures included iron status, haemoglobin or anaemia	Comments /Conclusions
					malaria; have haemoglobinopathies		

6.4 Discussion

Early childhood anaemia, continues to be a concern in remote Aboriginal and Torres Strait Islander settings across northern Australia[1, 2, 4, 3] My study of anaemia among young children of Far North Queensland identified developmental deficits at school age among children who had had early childhood anaemia.[10] Prevention of anaemia will support neurodevelopment in early life.[8] This review has assessed a range of interventions to identify those that could be effective in prevention of early childhood anaemia and any associated neurological deficits among Aboriginal and Torres Strait Islander children in remote settings in Australia.

The information presented here highlights the effectiveness of interventions using multi-micronutrient preparations that include iron for point-of-use fortification of complementary food, in prevention of iron deficiency and early childhood anaemia.[52, 55-57, 64] In addition, these multi-micronutrient preparations are effective in treating early childhood anaemia, safer than treatment with liquid iron and more acceptable to families.[56] The finding that such interventions are not only effective in raising haemoglobin levels but have functional benefits, with children showing improvements in indictors of neurodevelopment is particularly important.[61]

Educational interventions that promoted nutritious complementary foods had varying effects, with evidence for positive outcomes limited in resource-poor settings.[45, 46, 51] There was some evidence that meat-based foods, rich in haem iron, protect iron status in young children.[65] Meat-based complementary food(s) could be an option in remote Australian settings, depending on cost. The acceptability of alternative animal source foods has been assessed; in Indonesia a powder of dried beef and beef liver for fortification of complementary foods was acceptable, despite a fishy taste, while in the Congo cereal fortified with dried caterpillar has proven acceptable.[66, 67] Reports on the effectiveness of these products has for prevention of early childhood anaemia were not identified.

Another effective intervention identified here that can contribute to the prevention of early childhood anaemia is delayed clamping of the umbilical cord at birth.[44] Antenatal iron supplements have benefits for mothers but this review did not identify evidence of benefit in term of protection against early childhood anaemia.[43,41]

Mandatory fortification of flour with folate has been highly effective in preventing folate deficiency and neural tube defects among Aboriginal and Torres Strait Islander people and other Australians.[37, 38] In 2018, this intervention topped the list of the Australian Public Health Associations Top 10 Public Health Successes of the past twenty years.[68] However the effects of fortification of flour with iron appear more modest. In addition, concerns about fortification with iron have been flagged.[69, 70] Iron can have negative metabolic effects on individuals who have sufficient iron.[70] Instead targeted iron supplementation and/or fortification is recommended for those population groups with high needs.[69]

Some of the interventions described, focused on food security and dietary diversity, were not designed to address early childhood anaemia but theoretically could contribute to prevention of early childhood anaemia by improving dietary patterns. The store-based interventions and the subsidised fruit and vegetable boxes demonstrate that subsidies to improve affordability can result in increased fruit and vegetable consumption, if the subsidy is sufficient. However, despite the many health benefits of increased fruit and vegetable consumption, there was no apparent benefit in terms of improved iron status or reductions in anaemia prevalence in the one study where these outcomes were reported. It is clear that improvements in iron status and prevention of early childhood anaemia requires a different approach; nutrition promotion of optimal infant and young child nutrition combined with multi-micronutrient fortification of complementary food.

This review has used a methodical search strategy but is not a systematic review. One limitation therefore is that the quality of the reports included here has not been assessed. The review of nutrition interventions by Gwynn et al assessed the quality of most Australian studies as weak, including those reported here, mainly due to lack of blinding and control for confounding.[62] Six of the eighteen international publications were Cochrane reviews; the Cochrane review protocols are designed to provide high quality independent evidence.[71] Two of these Cochrane reviews reported on multi-micronutrient fortification of complementary food.[52, 55]

The World Health Organization identifies anaemia prevention as an Essential Nutrition Action but anaemia prevention does not appear to be on the public health nutrition agenda in Australia.[72] Only one - unpublished - report was identified for an Australian intervention

that focused on early childhood anaemia prevention among Aboriginal and Torres Strait Islander children.[54] Improved health and nutrition of mothers, infants and young children will also contribute to health through life, and support children to reach their full potential.[73] The absence of nutrition interventions to address early childhood anaemia is concerning especially as effective interventions exist, as shown in this review. In contrast, public health nutrition interventions to address dietary diversity and food insecurity in remote Aboriginal and Torres Strait Islander settings predominate, despite limited evidence of effect.[19, 29, 31]

Multi-micronutrient fortification of complementary food may not prevent all early childhood anaemia but can substantially reduce early childhood anaemia and improve early childhood development. Multi-micronutrient fortification can be embedded in initiatives to promote optimal infant and young child feeding.[51, 56] Maternal and child health services for Aboriginal and Torres Strait Islander Australians have demonstrated effectiveness in promoting optimal infant and young child feeding.[63] Early childhood anaemia prevention with provision of multi-micronutrient preparations to families for 'point-of-use' fortification of complementary food could perhaps be incorporated into these maternal and child health services. There is some evidence that integration of multi-micronutrient fortification into programs promoting optimal infant and young child nutrition can contribute to improvements in child feeding practices.[74] Each component of these combined strategies would reinforce the other. [51, 56, 74] These complementary actions are included in 'Essential Nutrition Actions' as 'double duty' actions effective in addressing multiple aspects of poor nutrition.[72]

In the absence of nutrition initiatives to prevent anaemia, health services in northern Australia focus on treatment of anaemia. Treatment protocols in remote community setting mean that many (~60%) infants and young children aged 6-23 months, would be prescribed at least 30mg of iron per day for 1-3 months to treat early childhood anaemia.[75-77] Instead the high prevalence of anaemia among young children of remote Aboriginal and Torres Strait Islander settings could be effectively addressed by use of multi-micronutrient preparations containing about 10 mg of iron with other micronutrients for home fortification of complementary food.[53]

Ideally addressing the underlying issues to improve food security and diet would assist prevent early childhood anaemia.[64] But until there are substantial changes in food security and dietary patterns in remote community settings, interventions using micronutrient preparations for prevention of early childhood anaemia offer an effective option that can be implemented relatively quickly.[64] There are challenges in operationalising such interventions – the lessons learnt in other settings have been recently summarised to guide future implementation.[49]

The current National Aboriginal and Torres Strait Islander Health Plan (p27) flags that *'delays in child development impact on education progress which in later life can impact on employment and opportunities, and consequently reinforces the social inequalities that produce health inequalities in subsequent generations*'.[73] Anaemia in early childhood is one reason for delays in child development.[8] Effective prevention of early childhood anaemia is feasible and offers the possibility of improved neurodevelopment in early childhood with subsequent improvements in educational achievement[61] – critical factors for Closing the Gap between Aboriginal and Torres Strait Islander people and other Australians.[78]

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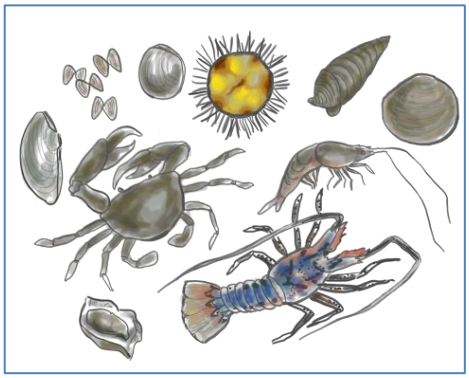
Foreword Chapter 7

In Chapter 7, I summarise the principal findings of this research and describe the strengths and weaknesses of the study. I raise some issues that require further investigation but also describe opportunities to improve nutrition and reduce anaemia in the first thousand days of life, through pregnancy to around age 2 years, among the Aboriginal and Torres Strait Islander mothers and their children in Far North Queensland – and elsewhere in Australia.

> *'...delays in child development impact of educational progress which in later life can impact of employment and opportunities, and consequently reinforce the social inequalities that produce health inequalities in subsequent generations'*
>
> The National Aboriginal and Torres Strait Islander Health Plan 2013-2023
>
> (Chapter 6 reference 73, p 27)



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Chapter 7 Discussion and Future Directions

7.1 Discussion

This research was undertaken to provide information on anaemia among Aboriginal and Torres Strait Islander children and their mothers in Far North Queensland (FNQ). The findings reported here show that among mothers more than half (54.5%) had anaemia in pregnancy [95% CI 52.4%, 56.7%] (Chapter 3).[1] A majority (61.3%) of children from remote FNQ communities had early childhood anaemia – anaemia at age 6-23 months [95%CI 57.7%, 64.9%] (Chapter 4).[2]

Subsequent assessment of childhood developmental indicators at school-age for a subset of these children who were assessed during the triennial Australian Early Development Census (AEDC), reported here in Chapter 5, demonstrated a detrimental association between anaemia and childhood development. Children who had had anaemia at age 6-23 months had more than double the risk of being included in the AEDC category of developmental vulnerability on two or more domains (OR 2.2 [1.1, 4.3] p = 0.020) at around age 5 years. These AEDC scores have been shown to be predictive of children's subsequent educational achievements in literacy and numeracy.[3]

These findings of high rates of anaemia among Aboriginal and Torres Strait Islander mothers and children are consistent with reports from similar settings in the Northern Territory and Western Australia.[4-7] Prior research in the Northern Territory and South Australia has identified perinatal factors associated with poor childhood developmental outcomes at school age, similar to those identified here.[8, 9] The research reported here had additional information in respect of early childhood anaemia and so could assess the association of anaemia in early life with developmental outcomes among these children. To our knowledge this is the first time this association has been demonstrated in remote northern Australia.

This research has limitations common to the use of routinely collected information for research purposes (Chapter 2).[10] One example was missing information though information completeness did improve over time.[11] Some information was not recorded by these electronic data collections, such as treatment for anaemia.[2, 11] This information gap

may explain one anomaly in the findings of this research, as anaemia in mothers was not associated with anaemia in their children. Effective treatment of anaemia of a pregnant mother may protect her unborn child from subsequent anaemia. The absence of treatment information meant that this hypothesis could not be tested. The limited geographic scope of the Ferret system where measurements of haemoglobin levels of children were recorded, meant that this information was available only for remote settings. A recent report from Western Australia found children age 6-59 months in non-remote localities had a prevalence of anaemia (35.5% anaemic) similar to that of children in remote localities (30.2% anaemic).[7] In this study however, information was missing for children in urban and rural areas.[11]

Another limitation is that this observational research cannot identify the cause of the anaemia reported here. As described in Chapter 1, iron deficiency is the 'usual suspect ' as the cause of anaemia in the first thousand days of life through pregnancy and up to age two years, due to the rapid growth including rapid expansion of blood volume during that time.[12 13] Two studies from similar setting in the Northern Territory provide evidence that iron deficiency was the cause of anaemia among pre-school and school aged children there.[14,15] However, this longitudinal retrospective cohort study cannot demonstrate if iron deficiency is the cause of anaemia among the mothers and children included in this study.

Similarly, this observational study cannot attribute the developmental disadvantage reported here to the early childhood anaemia experienced by these children. There are other causes of developmental delay in early childhood, that may co-exist with anaemia.[16] Multi-variable analysis was controlled for known factors (Chapter 5) but this adjustment cannot be made for unknown factors. However, these high rates of anaemia in pregnancy and early childhood among Aboriginal and Torres Strait Islander mothers and their children are indicative of widespread iron deficiency at a time of rapid neurodevelopment that offers a plausible explanation for developmental delay. Future work may provide evidence to support or disprove this explanation. In the meantime, it would be useful to assess if the same association between early childhood anaemia and developmental disadvantage at school age exists in other Australian jurisdictions where early childhood anaemia is prevalent.

There is evidence, described in Chapter 6, that interventions that are effective in raising haemoglobin levels and reducing early childhood anaemia are effective in supporting neurodevelopment in early life.[17] There have been concerns that the detrimental effects of iron deficiency at critical phases of neurodevelopment, may not be reversed by subsequent iron treatment.[18] The finding that interventions that are effective in treating anaemia have benefits for neurodevelopment means that anaemia treatment and/or prevention offers an opportunity *'to impact on neurodevelopment and brain function across the lifespan'.*[18]

Effective interventions for anaemia prevention are those that combine promotion of optimal nutrition for infants and young children with multi-micronutrient fortification of complementary food for infants from age 6 months and young children.[19,20,21] Such interventions are also effective for treatment of early childhood anaemia and both more acceptable and safer than the current practice of treatment with liquid iron preparations.[20]

It is an anomaly that current Australian nutrition programs with Aboriginal and Torres Strait Islander people rarely focus on anaemia prevention, despite WHO emphasis on anaemia prevention as an 'Essential Nutrition Action'.[22,23,24] There is legitimate concern that many Australians invest money in nutrient supplements for little health benefit rather than invest in healthy eating with proven health benefits.[25] Many participants (29%) in the 2011-12 Australian Health Survey had one or more nutrient supplement(s) on the previous day.[26] At the same time, Australians spent more on unhealthy food and beverage choices (53-64% of household food budgets) and less on healthy choices.[27] Such concerns however should never be a barrier to providing interventions including micronutrient supplementation and/or fortification to those population groups for whom there will be a benefit.[22]

International experience over two decades of interventions to prevent early childhood anaemia, and lessons learnt for effective implementation and evaluation have been recently compiled, so are available to guide implementation and evaluation of these interventions in Australian settings.[28] Equally it is important to assess ante-natal care practices in respect of the high rates of anaemia in pregnancy identified here, to evaluate if that anaemia is effectively addressed and if so, assess the benefit to these mothers and to their children.

7.2 Future Directions

This research provides information for consideration by the Aboriginal and Torres Strait Islander peoples of Far North Queensland and elsewhere in Australia. Any future initiatives must be preceded by engagement and detailed consultations with the communities concerned to ensure their lead role in deciding priorities and appropriate interventions.

In addition, this research provides information for consideration by policy makers, and health and education service providers. The National Aboriginal and Torres Strait Islander Health Plan 2013-2023 flags that;

'...delays in child development impact on educational progress which in later life can impact on employment and opportunities, and consequently reinforce the social inequalities that produce health inequalities in subsequent generations' (Chapter 6 reference 73, p.27)

There are many reasons why developmental delay in childhood may occur, of which anaemia is only one. But there are interventions to prevent early childhood anaemia and associated neurological disadvantage, that have proven to be effective in diverse settings.

Assuming community support, future initiatives could include;

- Work to make multi-micronutrient preparations (MNPs) suitable for babies and young children aged 6-23 months available – these products though widely used internationally are not currently available in Australia.
- Design and implementation of intervention(s) combining promotion of breastfeeding and healthy first foods with multi-micronutrient fortification of complementary food for infants from 6 months and young children in those Australian settings where the prevalence of early childhood anaemia is 20% or more.[12] These interventions could be incorporated into current maternal and child health services.
- Evaluation of those interventions to monitor implementation, and assess effectiveness in prevention of early childhood anaemia and the associated neurodevelopmental disadvantage at school age.
- Documentation and evaluation of current practices in respect of anaemia in pregnancy to assess if treatment of anaemia in pregnancy results in benefits for mothers, improved pregnancy outcomes and reduced anaemia in early life of children.

- Research into the association, if any, between early childhood anaemia and developmental vulnerability at school age in other Australian settings.

The Australian Government's commitment to Closing the Gap in health, education, social and economic indicators between Australian Aboriginal and Torres Strait Islander people and other Australians has been renewed as Closing the Gap Refresh. [29] The 2019 Closing the Gap report (p30) highlights the importance of maternal and child heath interventions '*to enhance positive and healthy early childhood development'* and emphasises the '*strong and consistent association between AEDC results and literacy and numeracy outcomes'*. However, the 2018 target to halve the gap in reading and numeracy has not yet been achieved.

Addressing anaemia of Australian Aboriginal and Torres Strait Islander children and their mothers – anaemia in the first thousand days of life - offers an opportunity that could improve early childhood development and subsequent educational achievement outcomes - and eventually employment outcomes. These initiatives could contribute to the Australian Government's commitment to Closing the Gap between Aboriginal and Torres Strait Islander peoples and other Australians. [29]

The future direction for this researcher therefore will be to continue to disseminate these research findings and to lobby for investment in improved nutrition and effective anaemia prevention and treatment among Aboriginal and Torres Strait Islander children and their mothers in the first thousand days of life, in Far North Queensland and elsewhere in Australia.

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Appendices

Appendix A: Human Research Ethics Committee Approvals

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Appendix B: Prior work – High Prevalence of Early Onset Anaemia Amongst Aboriginal and Torres Strait Islander Infants in Remote Northern Australia

AJRH The Australian Journal of Rural Health

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Aust. J. Rural Health (2018) ••, ••–••

Original Research

High prevalence of early onset anaemia amongst Aboriginal and Torres Strait Islander infants in remote northern Australia

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Abstract

Objectives: *To describe baseline growth and prevalence of anaemia in Aboriginal and Torres Strait Islander infants and young children enrolled in a nutrition promotion and anaemia prevention program in remote northern Australia.*

Design: *Retrospective review of most recent growth parameters and haemoglobin records during the 3 months prior to and 1 month after recruitment into a prospective study conducted between 25 May 2010 and 6 May 2012.*

Setting: *Primary health care clinics in six remote Aboriginal communities (east Kimberley, Western Australia (*n = *1); Northern Territory (*n = *4); Cape York, Queensland (*n = *1)).*

Participants: *Two hundred and sixty-two of the estimated 311 (84%) Aboriginal and Torres Strait Islander infants and young children aged 6–24 months residing in participating communities.*

Main outcome measures: *Prevalence of anaemia, stunting, underweight and overweight at recruitment.*

Results: *At recruitment, 42% of participants were anaemic, 18% stunted, 5% underweight and 5% overweight. Anaemia prevalence was higher than estimates (26–27%) in routine surveillance programs in remote communities and substantially higher than estimates (1.8–4.9%) in the general Australian population. One-quarter of participants were anaemic prior to 6 months of age.*

Conclusions: *The unexpectedly high prevalence of anaemia and stunting in these communities highlight the need for continued preventive health programs focused on ensuring adequate nutrition amongst infants, young children and their mothers. The early onset of anaemia and stunting suggests a comprehensive anaemia prevention approach is needed, including greater emphasis on maternal and pre-pregnancy health and nutrition to increase infants' iron stores at birth and sustain these to 6 months of age.*

KEY WORDS: *Aboriginal health, anaemia, child health, health service research, Indigenous populations.*

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Conflict of interest: Danielle Aquino (DA) was employed by The Fred Hollows Foundation during the project.

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Appendix C: Prior Work – Poor Nutrition from First Foods: A Cross-Sectional Study of Complementary Feeding of Infants and Young Children in Six Remote Aboriginal Communities Across Northern Australia

 DOI: 10.1111/1747-0080.12386

ORIGINAL RESEARCH

Poor nutrition from first foods: A cross-sectional study of complementary feeding of infants and young children in six remote Aboriginal communities across northern Australia

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Abstract

Aim: To describe the first foods of Aboriginal and Torres Strait Islander infants and young children who were recruited to a nutrition promotion and anaemia prevention program conducted from 2010 to 2012, in six remote communities across northern Australia.

Methods: Food records (24-hour diet history, food variety checklist) were completed on recruitment by interview with a parent or carer. Cross-sectional analysis assessed the proportion of participants consuming recommended and not-recommended foods and drinks and meeting recommendations for meal frequency and dietary diversity.

Results: Of 245 Aboriginal and Torres Strait Islander participants aged 6–24 months, 227 (92.7%) had a recruitment food record. On the previous day, most (67.4%) had breastmilk, nearly all (98.2%) ate solid food, but only 13% ate fruit, 33% had neither fruit nor vegetables, and 25% had sweet drinks. Children living in smaller households (3–5 people) were more likely to meet the criteria for frequency of meals than those living in larger households of 12–31 people (93% *vs* 78%, $P = 0.012$ for trend over household size). Only 30% met the criteria for dietary diversity. Where information was available (n = 91), dietary diversity was adequate more often in 'pay week' compared to 'not pay week' (31.3% *vs* 9.3%, $P = 0.007$).

Conclusion: Support for current beneficial breast-feeding practices and promotion of nutrient-dense complementary foods, need to be embedded in initiatives for improved family food security. Good nutrition in early life can reduce the disparity in health, education and economic status between Aboriginal and Torres Strait Islander peoples and other Australians.

Key words: Aboriginal, child, complementary feeding, dietary intake, infant.

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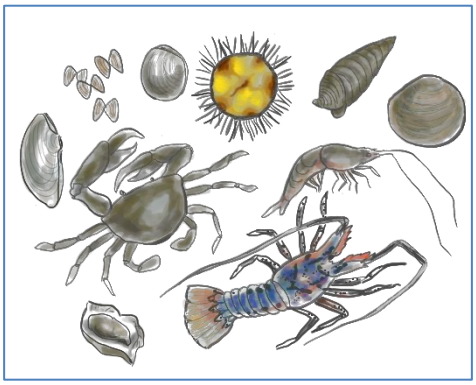
Appendix D: Traditional Aboriginal and Torres Strait Islander foods – illustrations by Julie Haysom

http://www.juliehaysom.com



Clockwise from pipis, shell (not identified), sea urchin, long muyu (mud whelk), large flat shell (wirril in Gunggandji language – language of Yarrabah/Cape Grafton area) prawn, painted crayfish, oyster, mudcrab, mussel

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from top; cheese fruit (morinda citrifolia – known as noni fruit in Pacific) peanut tree, lilly pilly, finger lime

from top; Cape plum, red berries, Davidson plum, beach almond, (Terminalia arenicola), white fruit native to Bamaga, brown berries – jamjam (terminalia sericocarpa), sugar bag

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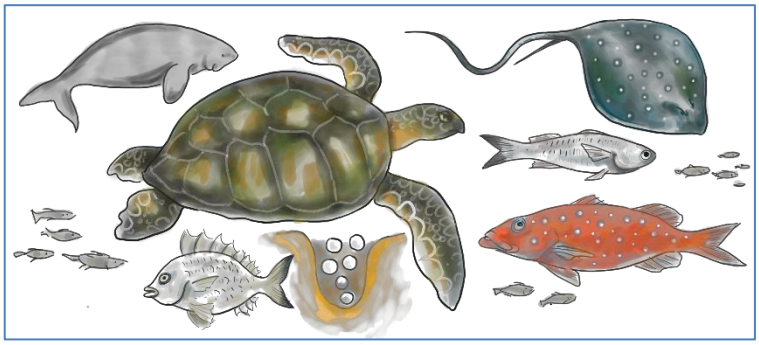
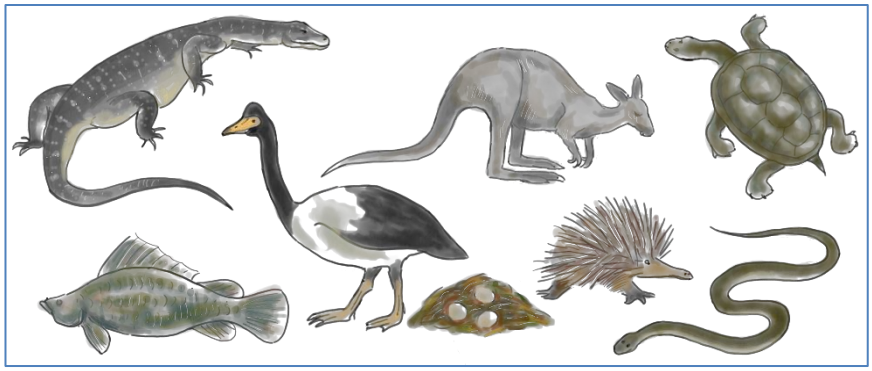
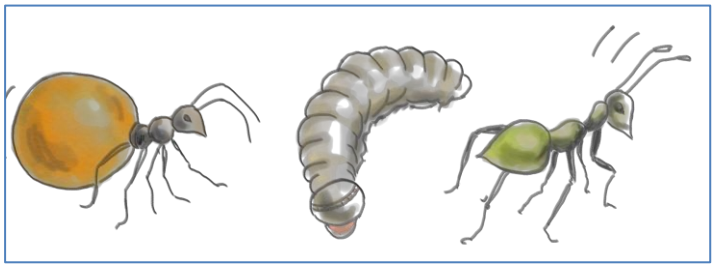


clockwise from dugong, green turtle (turtle eggs below) ray, mullet, coral trout, bream under turtle, small fish



Clockwise from goanna, kangaroo. long-necked turtle, olive python, echidna, magpie goose & eggs, barramundi



Honey ant, witchetty grub, green ant

From top; purple yam, pencil yam, ginger (*Alpinia caerulea* – Atherton Tablelands)