Maternal fetal programming of birthweight among Australian Aboriginal infants: a population-based data linkage study

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Summary

Background Low birthweight, which is common among Australian Aboriginal infants, has been found to persist across generations because of shared genetic and environmental factors and possibly fetal programming. Fetal programming refers to the response of a fetus to hostile uterine conditions with lifelong effects and possibly, in turn, providing a poorer uterine environment for future offspring. Fetal programming might have a greater effect in populations that have undergone rapid lifestyle transitions—for example, Indigenous populations. Disentangling causal effects is difficult, but family-based approaches could provide insights. We explored whether poor maternal fetal growth caused low birthweight in Aboriginal infants.

Methods In this data linkage study, we used linked administrative health records of 12 865 singleton Aboriginal infants born in Western Australia between 1980 and 2010 and their relatives (including siblings born in 2011). Electronic birth records included all births since 1980 with at least 20 weeks completed gestation or a birthweight of 400 g. We compared parental–offspring birthweight associations using three approaches—a regression analysis of the complete sample, adjusting for confounding variables; a comparison of the maternal–offspring and paternal–offspring associations; and a within-cousin group comparison. We used binary and continuous measures of birthweight. We categorised infants and their parents as small for gestational age (SGA) if their birthweight was below the first decile of birthweights for all singleton livebirths of the same sex and gestational age in Australia between 1998 and 2007.

Findings The relative risk (RR) of SGA birth was higher for infants with SGA mothers than for those with non-SGA mothers (RR 1·65, 95% CI 1·49 to 1·83), after adjusting for grandmaternal parity. After additional adjustment for maternal height, the risk remained higher for those with non-SGA mothers (RR 1·51, 1·36 to 1·68). The maternal birthweight Z score coefficient was 0·17 (95% CI 0·14 to 0·20), compared with 0·13 (0·10 to 0·16) for paternal birthweight, a difference of 0·03 (–0·01 to 0·08). In the cousin analysis, the maternal–offspring association was fully attenuated (0·00, 95% CI –0·05 to 0·06). Conditions in the current pregnancy were strongly associated with offspring birthweight Z score. Smoking was associated with a mean decrease of 0·39 (95% CI –0·45 to –0·34) in offspring birthweight Z score, drug misuse with a decrease of 0·31 (–0·43 to –0·20), and diabetes with an increase of 0·58 (0·39 to 0·77).

Interpretation We found little support for maternal fetal programming causing low offspring birthweight. The similar maternal and paternal influence on birthweight and our cousin analysis suggested transmission of genetic and environmental factors could explain much of the maternal–offspring birthweight association. Compared with other risk factors in the current pregnancy, fetal programming appears to have little or no role in the high numbers of infants with low birthweight among Aboriginal populations.

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Introduction

There has been a high proportion of low birthweights for generations among Aboriginal and Torres Strait Islander people (hereafter respectfully called Aboriginal).[1] Intrauterine growth restriction—when a fetus does not reach its growth potential—can be caused by poor health behaviours, morbidity, and complications during pregnancy. Low birthweight, a marker of intrauterine growth restriction, has been linked with many conditions that are relatively common among Aboriginal Australians, including type 2 diabetes, hypertension, and heart disease.[2]

Birthweight is also associated with the birthweight of the previous generation, possibly due to intergenerational transmission of genetic material that influences birthweight, transmission of environmental factors, and fetal programming, in which the responses of a fetus to a hostile uterine environment might affect that individual's health throughout their life (and, in turn, adversely affect their offspring's fetal environment; figure 1).[3]

An infant's birthweight is influenced by their own genes, as well as their mother's. The mother might be genetically predisposed to poor health or short stature,

Research in context

Evidence before this study

The developmental origins of health and disease hypothesis is an important framework that has emerged in recent decades. This hypothesis encompasses the concept of fetal programming in which, following an insult in utero, a fetus might undergo changes that have lifelong health effects. In turn, it has been further hypothesised that these changes could affect the uterine environment for the next generation. However, although maternal birthweight (an indicator of uterine environment) is clearly associated with offspring birthweight, the degree to which this is due to fetal programming is difficult to identify because of confounding by shared genetic and environmental factors.

For generations, low birthweight and poor postnatal health have been common among Aboriginal Australians. Fetal programming could explain the high burden of chronic disease seen among groups who have undergone rapid lifestyle transitions—for example, in rapidly developing nations and Indigenous populations.

We searched PubMed with no language restrictions for publicly available peer-reviewed studies pertaining to multigenerational birthweight and fetal programming published before May 8, 2018, with the search terms ("fetal programming" OR "developmental origins" OR "fetal origins") AND (("birth weight" OR "birthweight") OR ("intergenerational" OR "multigenerational" OR "transgenerational")). Our search revealed that non-human experiments have shown that fetal conditions in one generation can affect future generations; however, few studies have analysed data from human populations and results from these studies are mixed.

Some studies have found that paternal birthweight is almost as strongly associated with offspring birthweight as maternal birthweight, suggesting only a small role of the uterine environment in determining fetal growth. However, other studies have found a relatively small paternal–offspring birthweight association. Our search also found no previous studies attempting to disentangle fetal programming effects had been done in an Indigenous population.

Added value of this study

To our knowledge, our analysis is the first attempt to assess whether poor fetal growth in one generation affects fetal growth in a subsequent generation in an Indigenous population. Western Australian Aboriginal people have experienced rapid and extreme changes during the past century, including periods of insufficient nutrition, and analysis of their data could make a valuable contribution to the question of fetal growth.

Our analysis casts doubt on the hypothesis that the fetal health of Indigenous people continues to be affected by a historical legacy from maternal malnutrition in previous generations. Rather, any effect of fetal programming is likely to be minor compared with factors affecting the current pregnancy, such as maternal health behaviours and disadvantage.

Implications of all the available evidence

Based on the results of our study and the existing evidence, substantial improvements in Aboriginal perinatal health can be expected when maternal risk factors are addressed, unburdened by a mother's own fetal history.

therefore physically constraining fetal growth. Estimates of how much variation in birthweight is due to genetic factors vary widely. Two previous studies estimated 53%[4] and less than 10%.[5]

Furthermore, environmental factors that affect birthweight, such as smoking, can persist across generations and the effects of transgenerational poverty can expose the fetus to risks such as infection and malnutrition.

Finally, in-utero insults can cause structural and functional changes that affect adult health (fetal programming). For example, adults who were in utero during the Dutch famine of 1944–45 at the end of World War 2 had greater prevalence of cardiovascular and metabolic disease than did non-exposed adults.[6] Some fetal responses might be adaptive—for example, responses to insufficient nutrition, such as preference for a high-fat diet, might be beneficial in a postnatal environment of privation, but maladaptive when the actual environment is obesogenic.[2] Rats exposed to maternal malnutrition were more likely to develop metabolic disease, particularly with a high-fat diet.[7] Offspring of mothers with metabolic disease are also more likely to develop metabolic disease themselves[8] and, in this way, the effects of maternal fetal programming could be multigenerational. These fetal responses (the so-called thrifty phenotype) have been nominated as possible explanations for the high prevalence of metabolic disease in Indigenous populations and low-income and middle-income nations that have transitioned rapidly from traditional to more Western lifestyles.[8,9]

Fetal responses might be mediated by epigenetic changes. Studies have found evidence of epigenetic changes after poor uterine conditions, including in humans exposed to maternal smoking.[10,11] Transgenerational epigenetic inheritance has also been observed in some non-human species.[10] One exposure might cause epigenetic changes in two generations at once, since pregnant women carry both their own offspring and the germ cells of their future grandchildren.[12]

Non-human experiments have shown that exposure to malnutrition in one generation can affect a range of outcomes in two subsequent generations.[13] However, results are mixed for the outcome of birthweight. Pregnant rats (F0) fed poor quality diets have smaller pups (F1), but studies found that the birthweights of the following generation (F2) were unaffected,[14] although

another study found that certain subgroups weighed less.[15]

Such studies of humans are difficult because of the decades between generations and complex life histories, and results from natural experiments such as the Dutch famine of 1944–45 are inconsistent.[13] Most observational studies of multigenerational birthweights (in populations free from famine) have found positive associations between maternal and offspring birthweights.[13] However, it is difficult to quantify a causal relationship because of confounding by shared genetic and environmental factors, but we can gain insights by examining this association from different angles.

Parental–offspring birthweight associations can be compared. Shared genes that influence fetal growth are likely to result in equal positive associations for both parents. If maternal fetal programming affects offspring birthweight, the maternal–offspring association would be expected to exceed the paternal–offspring association.[16] Another approach involves comparing birthweights of cousins who share maternal grandparents. The cousins' mothers (F1) share many genetic and environmental factors, which can be controlled for by conditioning on their parents (the maternal grandparents; F0; figure 1). However, F1 sisters' intrauterine experiences (and birthweights) vary, and any remaining association between F1 and F2 birthweights would be due to either these intrauterine experiences or residual confounding.

The association between maternal height and offspring birthweight is well established. A mendelian randomisation analysis found that fetal genes largely explain this association and paternal height is almost as predictive of offspring birthweight as maternal height, which also suggests a genetic cause.[17,18] However, in a group of children born following egg donation, birthweight was more closely associated with the recipient's height than the donor's height, indicating maternal height might physically constrain fetal growth (figure 1).[19] Additionally, a lifetime of poor health could affect both maternal and offspring growth (figure 1).

The relative contributions of genetic factors, environmental factors, and fetal programming to birthweight could vary between populations. Aboriginal Australians are one of the world's oldest cultural groups, living in Australia for more than 50 000 years before colonisation. Colonisation of western Australia by Europeans began in 1829 and the Kimberley region in the northwest of Australia was not explored by Europeans until 1879.[20] Post-colonisation experiences of Aboriginal people included loss of resources, forced or poorly paid labour, population collapse, removal of children, and racism, leaving many Aboriginal communities and families impoverished and suffering the effects of intergenerational trauma.[20,21]

Today in the state of Western Australia, Aboriginal people make up 3% of the population of 2·5 million and 40% live in remote or very remote areas.[22,23] The life expectancy of Aboriginal men in Western Australia is 15·1 years lower than for non-Aboriginal men and for Aboriginal women is 13·5 years lower than for non-Aboriginal women.[22]

In this study of Aboriginal infants in Western Australia, we explored whether a poor fetal environment in one generation caused low birthweight in subsequent offspring by use of three analytical approaches—an analysis of the complete sample, adjusting for con-founding variables (approach one); a comparison of the parental–offspring associations (approach two); and a within-cousin group comparison (approach three).

Methods

Study design

In this data linkage study, birth records (from the Midwives Notification System), inpatient hospital records (from the Hospital Morbidity Data Collection), outpatient contacts with public community mental health services (from the Mental Health Information System), family relationships (from the Family Connections Project data), and birth registrations and records from the Western Australian Register of Developmental Anomalies (WARDA) for singleton Aboriginal infants born in Western Australia between 1980 and 2010 and their relatives (including siblings born in 2011) were linked probabilistically by the Western Australia Data Linkage Branch.

Electronic birth records included all births since 1980 with at least 20 weeks completed gestation or a birthweight of 400 g. Details of the mother, infant, maternal health, pregnancy, and birth were recorded, including infant sex, birthweight, and gestational age.

We used Indigenous identifiers on birth, hospital, birth registration, and WARDA records to identify Aboriginal infants using the previously published MSM+Family algorithm.[24] MSM refers to the multistage median algorithm,[25] which protects against false positive identifiers that are increasingly attached to individuals as more records are linked. +Family refers to the additional use of relatives' records, further protecting against false positives and negatives, and reducing the number of cases of missing Aboriginal status.[24]

The Western Australian Aboriginal Health Ethics Committee (reference 306-08/10) and the Western Australian Department of Health Ethics Committee (reference 2010/42) approved this study.

Procedures

We used binary and continuous measures of birthweight. We categorised infants and their parents as small for gestational age (SGA) if their birthweight was below the first decile of birthweights for all singleton livebirths of the same sex and gestational age in Australia from 1998 to 2007.[26] Infants were categorised as large for gestational age (LGA) if their birthweight was in the tenth decile.

We calculated birthweight Z scores with means and SDs for the same reference population[27] so that maternal–offspring and paternal–offspring birthweight associations

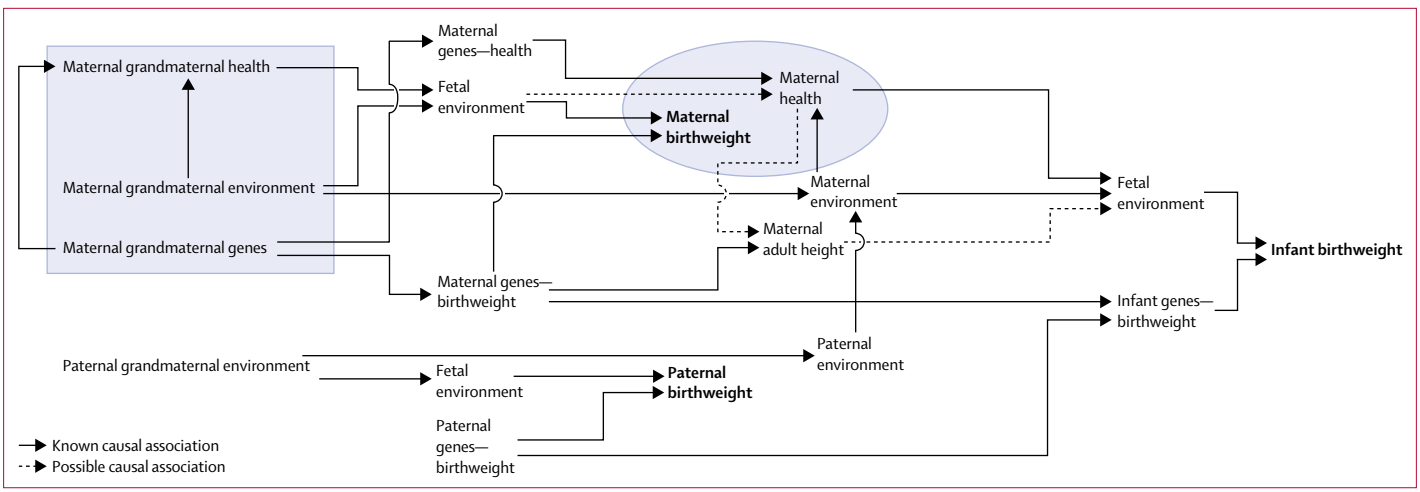

Figure 1: **Directed acyclic graph representing the possible causal associations between parental birthweight and infant birthweight**
Grandmaternal and maternal evironment includes individual factors (eg, maternal smoking during pregnancy) and community factors (eg, little access to high quality antenatal care) that affect birthweight and adult health. Maternal adult height and health might impose physical constraints on the growing fetus. We did not include paternal health or adult height as we assumed they do not directly cause low birthweight. Factors which are controlled for in analysis of cousins with shared maternal grandparents are in the shaded box. The shaded oval contains potential effects of fetal programming on the mother.

were scaled and comparable. We subtracted 4 weeks from gestational ages of 45 weeks or more, as an error in timing of the last menstrual period was more likely than an extremely prolonged pregnancy. Similarly, we added 4 weeks to the gestational age for 51 cases in which the infant or parental birthweight Z score was initially greater than 5. Birthweight Z scores less than –5 were for stillborn infants and were plausible birthweights.

Maternal height, behaviour, and health could confound the maternal–offspring birthweight relationship (figure 1). Therefore, we adjusted for maternal parity, maternal behaviours or assault (maternal smoking during pregnancy, alcohol misuse, drug misuse, and assault against the mother), and health conditions (diabetes, hypertension, obesity, herpes simplex virus infection, gonorrhoea, and other infections [syphilis, toxoplasmosis, rubella, cytomegalovirus, and varicella zoster virus]) that have previously been found to be associated with SGA births in a similar population.[1] We also adjusted for grandmaternal parity since this affects parental birthweight.

A mother was categorised as having a health condition if it was listed in her offspring's birth record or any of her hospital admissions during pregnancy. Using both these sources of information and broad disease categories improves case ascertainment without greatly increasing the false positive rate.[27] Diabetes included pre-existing and gestational diabetes, and hypertension included pre-existing hypertension complicating pregnancy, pre-eclampsia, and eclampsia. Diabetes and hypertension are well recorded in birth and hospital records.[27] For the International Classification of Disease codes used see the appendix.

See Online for appendix

Smoking during pregnancy has been comprehensively recorded in birth records since 1998. We categorised offspring as exposed to alcohol or drug misuse if there was an alcohol-related or drug-related diagnosis in their birth record or their mother's hospital admission or mental health records during the pregnancy. We categorised offspring as exposed to assault if their mother was admitted to hospital with an external injury code of violence any time from 2 years before the pregnancy until the birth, as we assumed violence before pregnancy was also a marker of assault during pregnancy. We did not include a similar assumption period for alcohol or drug misuse as women often reduce their consumption around pregnancy.

Statistical analysis

We compared infant and maternal characteristics for infants whose mothers were born SGA to infants whose mothers were not born SGA using Pearson's χ^2 tests for categorical variables and Wilcoxon rank-sum test for infant year of birth and maternal height. We used Poisson regression for the outcome of offspring SGA status and and linear regression for offspring birthweight Z scores, with a generalised estimating equation approach to account for clustering by mother with an independent covariance matrix and robust SEs. We compared results from the 20 complete datasets using Rubin's rules.[28] We used the multivariable fractional polynomial method to identify the form of the association between infant birthweight Z score and parental birthweight Z score. A linear term for paternal birthweight Z score was selected, but transformations of the maternal score resulted in the best fit. However, as the relationship was linear (from –4 to 2) for maternal birthweight Z score and our aim was to compare maternal and paternal birthweight Z score coefficients, we did not transform the maternal score (appendix).

Our initial model of the maternal–offspring birthweight association with the full sample (approach one) included maternal birthweight only. We then also adjusted for grandmaternal parity, maternal height, maternal behaviours or assault, and maternal parity. The final model also included maternal health conditions, which we added last as they could mediate the maternal–offspring birthweight relationship.

In our investigation of sample B (approach two), we also included paternal birthweight Z score and reparameterised maternal and paternal birthweight Z scores to calculate the difference in the coefficients for the maternal and paternal score.[18]

Finally, we compared cousins with shared maternal grandparents, similar to a within-sibling design, conditioning on maternal grandparents (approach three).[16] As cousins' mothers shared 50% of their genes on average, this design partly accounts for the genes confounding the maternal–offspring birthweight association. Environmental factors transmitted from grandparents to their daughters are also largely adjusted for. We only analysed the continuous outcome of birthweight Z score because restriction to discordant SGA status resulted in models with low power that provided no additional information.

We did sensitivity analyses on the subset of births with non-missing maternal height and births following at least two generations of Aboriginal mothers. We also analysed the full study sample with paternal SGA status categorised as SGA, not SGA, and missing.

Analyses were done with SAS, version 9.4, and R version 3.2.0.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and all authors were jointly responsible for the decision to submit for publication.

Results

Our study sample included 28 119 births between 1998 and 2010 in Western Australia, for which the infant and their full siblings were classified as Aboriginal, plus 890 Aboriginal children born in 2011 who had siblings among the 28 119 children born between 1998 and 2010. (figure 2). An estimated 7% of births from 2010 were missing, based on external data sources (appendix).

We excluded 15 776 (54%) of 29 009 infants whose mothers were missing a birth record as they were born before 1980 (14 014 [89%] births), from 1980 onwards but outside Western Australia (1497 [9%] births), or from 1980 onwards in Western Australia but they did not link to a record (165 [1%] births; figure 2). We could not determine maternal birthplace in the remaining cases (100 [1%] births). We then excluded 368 births (13%) with unknown gestational age for the infant or mother, leaving 12 865 births (sample A; figure 2). We linked 9091 children from sample A to their father. The father's identity was unknown if the birth was unregistered or his details were missing from the birth registration.[29,30] For 5504 (61%) of 9091 infants (sample B), the father had a Western Australia birth record with a valid gestational age (figure 2). Sample C consisted of 2609 infants from sample A who had at least one cousin with the same maternal grandparents.

Maternal height was missing for 5241 (41%) of 12 865 infants in sample A, 2327 (42%) of 5504 infants in sample B, and 1084 (42%) of 2609 infants in sample C, and for 4398 (27%) of 16 144 births between 1998 and 2011 that were not included in sample A. For 2821 (22%)

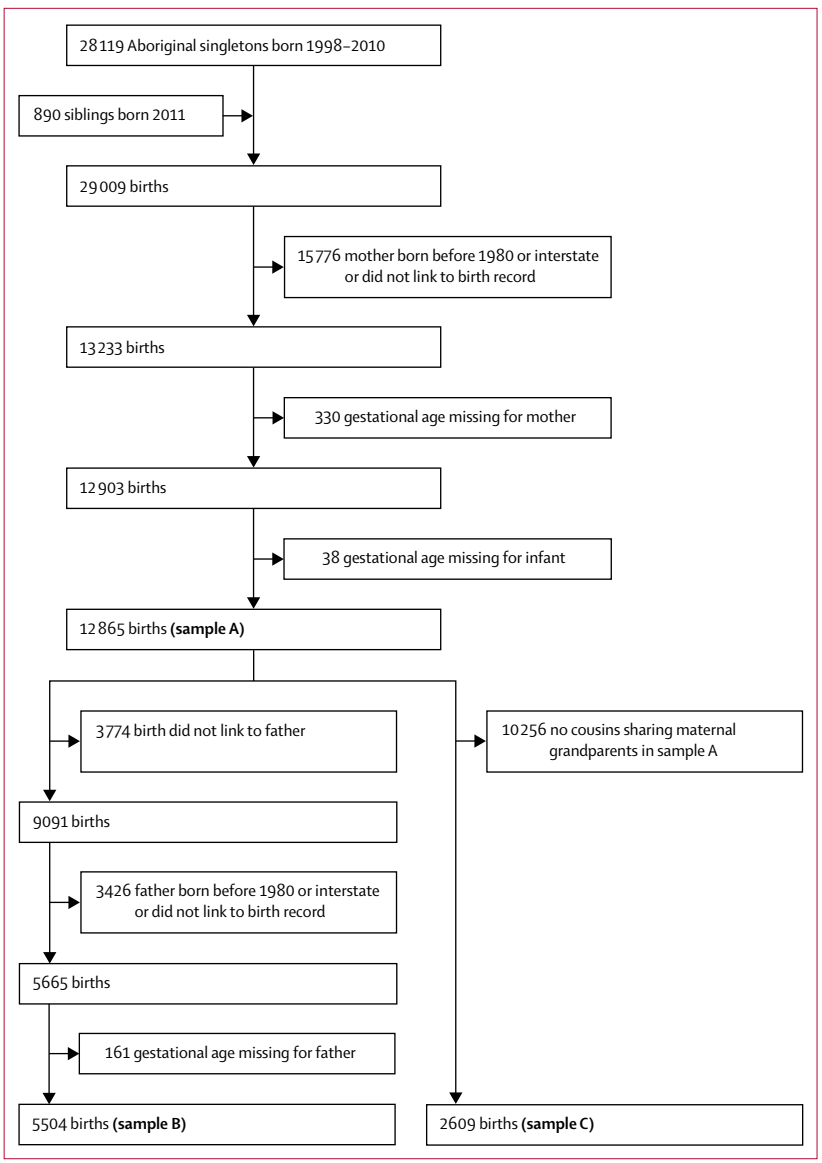

Figure 2: **Inclusion criteria for the study sample (sample A), the sample with birth records for both parents (sample B), and the sample of cousins with the same maternal grandparents (sample C)**

	Sample A (study sample)			Sample A (study sample; all births, n=12 865)	Sample B (both parents; all births, n=5504)	Sample C (cousins; all births, n=2609)	Excluded births (all births, n=16 144)
	Mother (F1) SGA (n=2105)	Mother (F1) not SGA (n=10 760)	p value				
Infant characteristics (F2)							
Year of birth	2006 (2003–09)	2007 (2004–09)	0·01	2006 (2004–09)	2007 (2005–09)	2006 (2004–09)	2003 (2000–06)
Maternal characteristics (F1)							
Age (years)			0·39				
12–15	194 (9%)	1023 (10%)		1217 (9%)	547 (10%)	245 (9%)	135 (1%)
16–19	650 (31%)	3470 (32%)		4120 (32%)	1900 (35%)	862 (33%)	851 (5%)
20–24	914 (43%)	4653 (43%)		5567 (43%)	2404 (44%)	1142 (44%)	3718 (23%)
25–29	338 (16%)	1562 (15%)		1900 (15%)	633 (12%)	347 (13%)	5224 (32%)
≥30	9 (<1%)	52 (<1%)		61 (<1%)	20 (<1%)	13 (<1%)	6216 (39%)
Original maternal height (cm)	160 (157–165)	164 (160–168)	<0·0001	163 (159–167)	163 (159–167)	163 (159–167)	163 (159–167)
Parity			0·72				
0	937 (45%)	4885 (45%)		5822 (45%)	2816 (51%)	1155 (44%)	2839 (18%)
1	612 (29%)	3108 (29%)		3720 (29%)	1569 (29%)	758 (29%)	3468 (21%)
≥2	556 (26%)	2767 (26%)		3323 (26%)	1119 (20%)	696 (27%)	9837 (61%)
Smoking during pregnancy	1044 (50%)	5010 (47%)	0·01	6054 (47%)	2169 (39%)	1203 (46%)	7644 (47%)
Drug abuse	179 (9%)	683 (6%)	0·0003	862 (7%)	312 (6%)	182 (7%)	1002 (6%)
Alcohol abuse	48 (2%)	230 (2%)	0·68	278 (2%)	49 (1%)	53 (2%)	553 (3%)
Assault against mother	147 (7%)	647 (6%)	0·09	794 (6%)	214 (4%)	172 (7%)	1283 (8%)
Diabetes	95 (5%)	411 (4%)	0·13	506 (4%)	173 (3%)	106 (4%)	1402 (9%)
Hypertension	219 (10%)	1069 (10%)	0·51	1288 (10%)	561 (10%)	258 (10%)	1572 (10%)
Obesity	37 (2%)	199 (2%)	0·77	236 (2%)	81 (1%)	41 (2%)	408 (3%)
Gonorrhoea	29 (1%)	94 (1%)	0·03	123 (1%)	27 (<1%)	23 (1%)	70 (<1%)
Herpes	29 (1%)	86 (1%)	0·01	115 (1%)	41 (1%)	16 (1%)	216 (1%)
Other infections	14 (1%)	40 (<1)	0·06	54 (<1)	8 (<1)	10 (<1)	96 (1%)
Grandmaternal characteristics (F0)							
Parity			<0·0001				
0	740 (35%)	3176 (30%)		3916 (30%)	1706 (31%)	546 (21%)	..*
1	567 (27%)	2681 (25%)		3248 (25%)	1498 (27%)	648 (25%)	..*
≥2	798 (38%)	4903 (46%)		5701 (44%)	2300 (42%)	1415 (54%)	..*

Data are median (IQR) or n (%). p values are from Pearson's χ^2 tests for categorical variables and Wilcoxon rank-sum test for continuous variables. SGA=small for gestational age. *For almost all births between 1998 and 2011 that were not included in sample A, the mother did not link to a Western Australia birth record from 1980 onwards and grandmaternal parity was not available.

Table 1: **Infant and maternal characteristics for births in each of the three samples, and Aboriginal births in Western Australia between 1998 and 2011 that were not included in sample A**

infants in sample A, a sibling's birth record listed their mother's height. We imputed the remaining 2420 (19%) unknown heights using multiple imputation with chained equations. We created 20 complete datasets (appendix).

The maximum maternal age in the study sample (sample A) was 31 years. 9 (<1%) of 2105 mothers who were SGA and 52 (<1%) of 10 760 mothers who were not SGA in sample A were aged 30 years or older, compared with 6216 (39%) of 16 144 excluded births whose mothers were predominantly born before 1980 (table 1). Reflecting this age difference, 937 (45%) of 2105 and 4885 (45%) of 10 760 sample A births were to nulliparous mothers, compared with 2839 (18%) of 16 144 excluded births, and maternal diabetes was less common among sample A (506 [4%] of 12 865 births) than among excluded births (1402 [9%] of 16 144 births).

In sample B, paternal age was also capped at 31 years, which further reduced the mean maternal age. Mothers in sample B were less likely to smoke, misuse drugs and alcohol, or have infections compared with mothers in sample A, with a difference of 8 percentage points for smoking and 1 percentage point for the other risk factors (table 1). These differences might be because of their youth and differences between infants (and their mothers) on the basis of whether births are registered and, if registered, whether the father's details are listed on the registrations.[29,30] However, sample C and sample A

had similar distributions of maternal demographic characteristics and health.

The study sample (sample A) were more likely to be SGA and had a lower mean birthweight Z score than did the reference population of all Australian infants born alive from 1998 to 2007.[23] This predominantly non-Aboriginal reference population was 10% SGA, with a mean birthweight Z score of 0, by definition, whereas 2140 (17%) of 12 865 infants in sample A were SGA, 856 (7%) were LGA and the mean birthweight Z score was –0·28 (SD 1·04). The mean birthweight was 3146 g (SD 654) for infants, 3161 g (543) for mothers, and 3289g (563) for fathers.

Mothers born SGA were more likely to smoke, misuse drugs, or have infections while pregnant than were non-SGA mothers, and their median height was lower (table 1). Incidence of diabetes, hypertension, obesity, and infection were similar for SGA and non-SGA mothers. Even after restricting to mothers born weighing less than 4000 g to account for the U-shaped association between birthweight and gestational diabetes,[31] the absolute difference in the prevalence of diabetes among SGA and non-SGA mothers was less than 1%.

Maternal height explained some of the relationship between maternal SGA and infant SGA (table 2). The relative risk (RR) of SGA birth was higher for infants with SGA mothers than for those with non-SGA mothers (RR 1·65, 95% CI 1·49–1·83), after adjusting for grandmaternal parity. After additional adjustment for maternal height, the risk remained higher for those with non-SGA mothers (1·51, 1·36–1·68). Inclusion of maternal height might allow for partial adjustment for genetic factors and maternal health during the mother's growth years.

We observed a strong association between maternal and offspring birthweight Z score, with an increase of one SD in maternal birthweight predicting a mean increase of 0·17 (95% CI 0·14 to 0·20) SDs in offspring birthweight (model 7; table 2). The father–offspring birthweight association was similar (0·13, 0·10 to 0·16), suggesting environmental and genetic factors shared by parents and offspring could explain much of the birthweight association. The positive difference in the β coefficients (0·03, –0·01 to 0·08) provides some support for a greater maternal than paternal association, although the CI was wide and consistent with equal associations.

We investigated the associations between offspring birthweight and the covariates included in model 12 (table 3). Smoking was associated with a mean decrease of 0·39 (95% CI –0·45 to –0·34) in offspring birthweight Z score, drug misuse with a decrease of 0·31 (–0·43 to –0·20), and diabetes with an increase of 0·58 (0·39 to 0·77).

Although maternal behaviour or assault and maternal health only slightly confounded the maternal–offspring birthweight association (table 2), they were important predictors of offspring birthweight (table 3).

	Approach	Adjusted for maternal birthweight*	Adjusted for paternal birthweight*	Adjusted for grandmaternal parity†	Adjusted for maternal height	Adjusted for maternal parity and behaviour or assault‡	Adjusted for maternal health during pregnancy§	Adjusted for maternal grandparents	Maternal SGA¶	Paternal SGA¶	Maternal Z score‖	Paternal Z score‖	Difference in parental Z scores‖
1	1	Yes	No	No	No	No	No	No	1·62 (1·47 to 1·80)	..	0·16 (0·14 to 0·19)	..	..
2	1	Yes	No	Yes	No	No	No	No	1·65 (1·49 to 1·83)	..	0·17 (0·15 to 0·19)	..	..
3	1	Yes	No	Yes	Yes	No	No	No	1·51 (1·36 to 1·68)	..	0·14 (0·11 to 0·16)	..	..
4	1	Yes	No	Yes	Yes	Yes	No	No	1·48 (1·34 to 1·64)	..	0·13 (0·11 to 0·16)	..	..
5	1	Yes	No	Yes	Yes	Yes	Yes	No	1·48 (1·34 to 1·64)	..	0·13 (0·11 to 0·16)	..	..
6	2	No	Yes	No	No	No	No	No	..	1·44 (1·22 to 1·71)	..	0·14 (0·11 to 0·17)	..
7	2	Yes	No	No	No	No	No	No	1·65 (1·39 to 1·95)	..	0·17 (0·14 to 0·20)	..	..
8	2	Yes	Yes	No	No	No	No	No	1·65 (1·39 to 1·95)	1·44 (1·22 to 1·71)	0·17 (0·14 to 0·20)	0·13 (0·10 to 0·16)	0·03 (–0·01 to 0·08)
9	2	Yes	Yes	Yes	No	No	No	No	1·65 (1·40 to 1·96)	1·45 (1·23 to 1·72)	0·17 (0·14 to 0·20)	0·14 (0·11 to 0·17)	0·03 (–0·01 to 0·08)
10	2	Yes	Yes	Yes	Yes	No	No	No	1·54 (1·29 to 1·83)	1·45 (1·22 to 1·71)	0·14 (0·11 to 0·17)	0·13 (0·11 to 0·16)	0·01 (–0·04 to 0·05)
11	2	Yes	Yes	Yes	Yes	Yes	No	No	1·50 (1·26 to 1·77)	1·44 (1·22 to 1·70)	0·14 (0·11 to 0·17)	0·13 (0·10 to 0·16)	0·00 (–0·04 to 0·05)
12	2	Yes	Yes	Yes	Yes	Yes	Yes	No	1·49 (1·26 to 1·77)	1·46 (1·24 to 1·73)	0·14 (0·11 to 0·17)	0·13 (0·10 to 0·16)	0·01 (–0·03 to 0·05)
13	3	Yes	No	No	No	No	No	No	..	..	0·16 (0·12 to 0·21)	..	..
14	3	Yes	No	Yes	No	No	No	No	..	..	0·17 (0·12 to 0·22)	..	..
15	3	Yes	No	Yes	No	No	No	Yes	..	..	0·00 (–0·05 to 0·06)	..	..
16	3	Yes	No	Yes	Yes	No	No	Yes	..	..	0·00 (–0·06 to 0·05)	..	..
17	3	Yes	No	Yes	Yes	Yes	No	Yes	..	..	0·00 (–0·05 to 0·06)	..	..
18	3	Yes	No	Yes	Yes	Yes	Yes	Yes	..	..	0·00 (–0·05 to 0·06)	..	..

SGA=small for gestational age. *SGA or Z score. †On the maternal side, paternal side, or both, depending on whether maternal birthweight, paternal birthweight, or both were in the model. ‡Smoking, alcohol misuse, drug misuse, and assault against the mother. §Diabetes, hypertension, obesity, gonorrhoea, herpes, and other infections (syphilis, toxoplasmosis, rubella, cytomegalovirus, and varicella zoster). ¶Data are relative risk (95% CI). ‖Data are β (95% CI).

Table 2: **Estimates from different models of associations between parental and offspring SGA births and birthweight Z scores**

	Infant SGA status*	Infant birthweight Z score†
Maternal SGA status	1·49 (1·26–1·77)	..
Paternal SGA status	1·46 (1·24–1·73)	..
Parental birthweight Z scores		
Mean of coefficients	..	0·13 (0·11 to 0·15)
Difference in coefficients	..	0·01 (–0·03 to 0·05)
Maternal height (per cm increase)	0·98 (0·97–0·99)	0·02 (0·01 to 0·02)
Maternal behaviour or assault		
Smoking	1·89 (1·64–2·17)	–0·39 (–0·45 to –0·34)
Drug misuse	1·56 (1·27–1·90)	–0·31 (–0·43 to –0·20)
Alcohol misuse	1·42 (0·93–2·17)	–0·26 (–0·49 to –0·03)
Assault against mother	1·48 (1·12–1·94)	–0·24 (–0·38 to –0·10)
Maternal health		
Diabetes	0·51 (0·29–0·89)	0·58 (0·39 to 0·77)
Hypertension	1·42 (1·18–1·70)	–0·07 (–0·16 to 0·03)
Obesity	0·31 (0·10–0·92)	0·34 (0·13 to 0·55)
Gonorrhoea	1·65 (0·89–3·07)	–0·21 (–0·64 to 0·21)
Herpes	1·06 (0·48–2·36)	0·09 (–0·24 to 0·43)
Other infections‡	1·86 (0·78–4·39)	–0·29 (–1·50 to 0·91)
Maternal parity§		
1	0·68 (0·58–0·79)	0·25 (0·19 to 0·30)
≥2	0·57 (0·47–0·70)	0·27 (0·20 to 0·34)
Maternal grandmaternal parity§		
1	0·93 (0·77–1·12)	–0·01 (–0·08 to 0·07)
≥2	1·02 (0·87–1·21)	–0·07 (–0·14 to 0·00)
Paternal grandmaternal parity§		
1	1·10 (0·91–1·32)	–0·08 (–0·15 to 0·00)
≥2	1·05 (0·88–1·24)	–0·05 (–0·12 to 0·02)

SGA=small for gestational age. *Data are relative risk (95% CI). †Data are coefficient (95% CI). ‡Other infections refers to syphilis, toxoplasmosis, rubella, cytomegalovirus, and varicella zoster. §Nulliparity used as a reference.

Table 3: **Associations of SGA birth and birthweight Z score with parental measures of birthweight and other characteristics from model 12 in table 2**

In our analysis of cousins sharing the same maternal grandparents, the maternal–offspring birthweight association was fully attenuated (0·00, 95% CI –0·05 to 0·06; model 15; table 2).

Sensitivity analyses of two subsamples, infants with maternal height recorded on their birth record and infants with Aboriginal mothers and maternal grandmothers, led to the same conclusions as the main analyses; the coefficients for parental birthweight Z score and their difference differed by 0·02 or less from the results in table 2. In the third sensitivity analysis of the full study sample, with paternal SGA status categorised as SGA, not SGA, and missing, in the fully adjusted model the relative risks for maternal SGA status and paternal SGA status only differed by 0·02 from model 12 in table 2 (data not shown).

We calculated differences in the birthweights of the mothers of cousins in sample C. For all sister pairs, the median difference in birthweight Z score was 0·78 (IQR 0·36–1·32).

Discussion

In this study of Aboriginal infants born in Western Australia between 1998 and 2011, we observed a strong association between maternal and offspring birthweights, which appeared to be largely due to intergenerational transfer of genetic and environmental factors. We found little evidence that fetal programming has a role, although our results were consistent with a small effect. By contrast, the proximal and modifiable factors of maternal behaviour or assault and maternal health during pregnancy were strongly associated with offspring birthweight.

Fetal programming occurs when adverse uterine conditions cause changes to a fetus. Diabetes and hypertension have been linked to low birthweight.[2] If fetal programming in one generation affected birthweight in the next, and this was mediated by health during pregnancy, we would expect poorer maternal health for births to SGA mothers than for births to non-SGA mothers. However, the absolute differences in the prevalence of diabetes and hypertension were minimal in our study (<1%), even after restriction to mothers born weighing less than 4000 g to account for the U-shaped association between birthweight and gestational diabetes (data not shown).[31] Such a small increase in risk suggests that any effects in the next generation would be negligible.

We also expected a stronger maternal–offspring birthweight association than paternal–offspring birthweight association if maternal fetal programming affected offspring birthweight. The regression coefficient for paternal birthweight encompasses genetic and environmental factors shared with the infant, while the coefficient for maternal birthweight also encompasses physical constraints from poor maternal health and maternal height, caused by maternal fetal programming and genetic factors. The difference between the coefficients for maternal birthweight Z score and paternal birthweight Z score was only 0·03 (95% CI –0·01 to 0·08). Although this result is consistent with fetal programming involvement, it offers little evidence of any great influence. The difference would be closer to 0 if some fathers were incorrectly identified or environmental factors transmitted down the maternal line were more influential than those transmitted down the paternal line.

Finally, studies of cousins with shared maternal grandparents control for the genetic and environmental factors shared by their mothers, which confounded our analyses of the complete study sample. If fetal programming played a part in birthweight we would expect an association between maternal and offspring birthweight after conditioning on maternal grandparents, but no association was found (β 0·00, 95% CI –0·05 to

0·06). This result indicates that the different uterine conditions in sisters, measured by the proxy of birthweight, have little or no effect on the birthweight of their offspring. This result could be a false null if the sisters' birthweights were too similar.[16] However, the birthweights of the sisters were highly variable. The median difference in birthweight Z score for all pairs of sisters was 0·78 (IQR 0·36–1·32). Some of this difference could be due to differing grandmaternal parities, but the predicted decreases in birthweight Z score due to parity in our models were much lower (eg, 0·25 for parity of one compared to nulliparous in model 12). A finding of no association in such fixed effects models provides strong evidence of no causal association.[32]

It is possible that maternal fetal programming leads to both small offspring (eg, mediated by maternal hypertension) and large offspring (eg, mediated by maternal diabetes), leading to the negative results seen in our study. However, this explanation seems unlikely, since maternal hypertension and diabetes were unrelated to maternal SGA status and the proportion of LGA offspring was only 7%.

Accurately modelling a causal relationship between a mother's own fetal environment and offspring birthweight is complex and our approaches have limitations. However, if multiple approaches to the same question have different biases, yet converge on the same conclusion, we can have greater confidence in that conclusion.[32,33]

Mothers who were born SGA were more likely to smoke, misuse drugs, or have infections while pregnant than those who were not born SGA. The small size at birth of these mothers might have resulted from their own mother's health behaviours or other risks associated with low-income communities. Many Aboriginal communities have widespread poverty, low levels of education, social exclusion, and multigenerational trauma, all of which are determinants of substance use and health,[21,22] and therefore poor health behaviours and deprivation might be perpetuated across generations.

Some Aboriginal perinatal outcomes have improved in recent decades, including a drop in the neonatal death rate, possibly due to improved neonatal care and transport and more women giving birth in hospitals.[34] However, numbers of infants with low birthweight have remained static in Western Australia over the past three decades.[35] In recent years, new programmes have been introduced with the aim of reducing substance use by pregnant women and improving antenatal care—for example, the New Directions: Mothers and Babies Services programme.[36] Long-term improvements in Aboriginal health require widespread shifts in the social determinants of health. Community empowerment and reductions in poverty are essential.[37]

A major limitation of this study is that SGA and birthweight Z score are only markers of uterine conditions. Another limitation is the small number of older mothers, who are more likely to have hypertension and diabetes. However, Aboriginal mothers tend to be young—maternal age was only 30 years or older for 21% of births in the study sample and excluded births combined (table 1). Sample B was even less representative of Aboriginal infants from Western Australia. However, an analysis of the full study sample with paternal SGA categorised as SGA, not SGA, and missing SGA had similar results to the analysis of Sample B only. Furthermore, the parents listed on an infant's birth registration might not be the biological parents—for example, following incorrect attribution of paternity or egg donation. Finally, this study investigated birthweight and our findings cannot be extrapolated to conclude that no vulnerabilities are transmitted transgenerationally.

For this study we used a unique dataset which allowed for family-based approaches, which can provide information when genetic data are unavailable. Western Australia is the only Australian state with a database of extended family links. The investigated population was also important, as researchers have hypothesised that Indigenous populations might be particularly affected by fetal conditions and Western Australia's Aboriginal peoples were among the last in the country to be colonised. If maternal fetal programming has an important role in infant birthweight we would expect to observe it in this population, following generations of poor birth outcomes and—if the thrifty phenotype hypothesis has merit—a recent history of malnutrition and rapid lifestyle changes. Few other studies of intergenerational birthweights in Indigenous populations have been done and, to our knowledge, none has unpicked these complex associations.

In conclusion, the results of our study suggest that a mother's own fetal environment is relatively unimportant compared with other risk factors during pregnancy. Therefore, substantial improvements in perinatal health are possible within a single generation if risk reduction approaches that are effective among Aboriginal women, families, and communities are identified and supported.

Contributors

All authors developed the research question. AJG did the data analysis and wrote the first draft of the Article. JMS, BJM, and SJE supported the data analysis and commented on the drafts of the Article. SJE obtained the funding. BJM and SJE obtained the data.

Declaration of interests

We declare no competing interests.

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