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Anaemia of Pregnancy, Perinatal Outcomes and Children's Developmental Vulnerability: a Whole-of-Population Study

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Abstract

Background: There is limited longitudinal data from high-income countries on the sequelae of anaemia during pregnancy. The aim of this study is to examine whether anaemia of pregnancy is associated with adverse perinatal outcomes and with children's developmental vulnerability.

Methods: We conducted a population-based study to link routinely collected government administrative data that involved all live births in the state of South Australia 1999–2005 ($n = 124\,061$) and a subset for whom developmental data were collected during a national census of children attending their first year of school in 2009 ($n = 13\,654$). Perinatal outcomes were recorded by midwives using a validated, standardised form. Development was recorded by schoolteachers using the Australian Early Development Index (AEDI). Children in the lowest 10% of AEDI scores are indicative of developmental vulnerability.

Results: There were 8764/124 061 (7.1%) cases of anaemia. After adjustment for a range of potentially confounding factors, anaemia of pregnancy was associated with a higher risk of fetal distress [incident rate ratio (IRR) 1.20 [95% CI 1.13, 1.27]] and preterm birth <37 weeks gestation (IRR 1.23 [1.15, 1.31]), slightly higher birthweight [14 g (2, 26)] and newborns were less likely to require resuscitation (IRR 0.94 [0.91, 0.097]). Anaemia of pregnancy was not associated with children's developmental vulnerability after adjustment for maternal, obstetric and sociodemographic covariables, either in complete case analyses ($n = 11\,949$) or after imputation for missing data ($n = 13\,654$).

Conclusions: Anaemia of pregnancy is associated with perinatal complications but not with children's developmental vulnerability at school entry.

Keywords: *anaemia, pregnancy outcome, child development.*

The World Health Organisation has estimated the prevalence of anaemia of pregnancy to be 15.2% among women in the UK, 12.4% in Australia, and 5.7% in the USA.[1] Anaemia has been associated with a wide range of pregnancy complications including perinatal mortality, lower gestational age, and birthweight.[2] Although anaemia has multiple aetiologies, iron deficiency is a major cause of anaemia for otherwise well-nourished women from high-income countries.[3–5] Consequently, some countries have introduced routine supplementation of pregnant women with iron. However, it has been suggested that routine iron supplementation could increase the risk of complications for pregnant women who are iron replete.[6,7] In Australia, routine iron supplementation is not endorsed for pregnant women, instead iron supplements are recommended only upon clinical indication.[3,4,8]

Iron is considered important for fetal neural development. Studies in primates show that iron deficiency, particularly during the third trimester, results in permanent changes to offspring behaviour and activity.[9] Supporting evidence from Finland showed that lower haemoglobin during pregnancy was associated with poorer school achievement,[10] but haemoglobin was measured in 1966, and we have since witnessed improvements in routine perinatal care, screening, and treatment of anaemia due to iron deficiency. Therefore, it is unclear whether there are lasting effects of anaemia of pregnancy on child development in contemporary settings.

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In this study, we linked health and educational data sets held by Australian government departments to examine; (1) the extent to which anaemia of pregnancy is linked to a range of perinatal outcomes, and (2) the association between anaemia of pregnancy and children's developmental vulnerability.

Methods

Approval for this study was given by the ethics committees of the University of Adelaide and South Australian Department of Health, as well as data custodians (representatives from the government departments). As this study involves de-identified data routinely collected by government, consent was not obtained from participants.

Participants

The study included all live births in the state of South Australia 1999–05, using the routine collection of perinatal data and the 2009 national census of children's developmental vulnerability for children attending their first year of full-time schooling.

Data linkage process

Data linkage was conducted by SA-NT DataLink (https://www.santdatalink.org.au). Data matching was conducted on basic identifiers (e.g. name, age, sex, and address). Data custodians provided identifiers to SA-NT DataLink, who developed a probabilistic linkage algorithm to match individuals in different government data sets using their identifying information. Quality assurance checks and clerical review were conducted to minimise mismatches. SA-NT DataLink assigned each individual a unique project identifier and returned the data sets to the custodians. The custodians attached the identifier to their data sets, removed all personal identifying information, and forwarded the de-identified health or education data for analysis.

In <0.5% of cases, the information in the data sets did not uniquely identify each case, resulting in a small number of duplicates ($n = 64$ in the perinatal and $n = 71$ in the education data sets). All duplicates were omitted prior to analysis.

Exposure: anaemia of pregnancy

Midwives and neonatal nurses completed the Supplementary Birth Record (SBR) form, which is collated by the Pregnancy Outcome Unit, South Australian Department of Health. Completion of the SBR is mandatory and is accompanied by a companion document that describes how to complete the form. The use of the SBR form, which includes correctly documenting a diagnosis of anaemia of pregnancy, has been validated against an audit of medical records.[11] The SBR form and the associated data are designed for collection of perinatal data for government use and consequently, the trimester and severity of the anaemia is not collected.

Current practice guidelines recommend that women be screened for anaemia at their first antenatal visit and at 28 weeks gestation.[4] Anaemia of pregnancy was defined as haemoglobin <110 g/L in the first trimester, or <105 g/L in the second or third trimesters. Upon a diagnosis of anaemia, usual practice involves recommending supplementation with 40–80 mg/day of elemental iron and dietary advice. Iron supplementation is recommended because iron deficiency is considered the most common cause of anaemia for pregnant Australian women.[4] Due to limitations of the data set, we were unable to distinguish the cause of anaemia or whether women took iron supplements.

Outcomes: perinatal

Perinatal outcomes are recorded on the SBR form according to established criteria documented in the SBR manual. Fetal distress is documented according to pH from scalp clip and/or abnormal cardiotocograph. Infants weighing <2.5 kg are defined as low birthweight (LBW). Children born <37 weeks gestation (according to ultrasound, menstrual history, or neonatal examination) were defined as preterm. Birthweight-for-gestational age z-scores were calculated using sex-specific weights and gestational ages of Australian children.[12] We were unable to examine associations between anaemia of pregnancy and perinatal deaths because these data were not included in our data set for confidentiality reasons. Resuscitation at birth was categorised as: none, aspiration, oxygen, intermittent positive pressure ventilation (IPPV), or other.

Outcomes: Australian Early Development Index (AEDI)

The AEDI is a holistic measure of children's development at school entry (median age 5 years), which demonstrates predictive validity for later school achievement.[13–15] In 2009, the AEDI was collected by schoolteachers during a national census of children attending their first year of school, conducted by the Australian Government Department of Education.[16] The AEDI includes 95 questions that result in scores ranging 0–10 across five domains: physical health and wellbeing, language and cognitive skills, emotional maturity, social competence, and communication and general knowledge. Responses are age standardised and children in the lowest 10% of the national population distribution of AEDI scores for each domain are categorised as developmentally vulnerable.[13] The AEDI is not normally distributed and its use as a binary variable is in accordance with national reporting practices.[13] Children were also categorised according to whether they were vulnerable on ≥1 domain.

Potential confounders

Potential confounders were selected *a priori* based on a causal model of the effect of anaemia on perinatal outcomes on children's developmental vulnerability, using directed acyclic graphs.[17] Potential confounders obtained from the perinatal data set included: maternal age, smoking during pregnancy (yes, no), plurality (singleton, multiple), parity (nulliparous, one previous birth, or ≥2 previous births), number of antenatal visits (≤5, 6–12, or ≥13 visits), inter-pregnancy interval (first pregnancy, <1 year, or ≥1 year), maternal and paternal occupation, and postcode. Maternal and paternal occupation were coded according to the major skill groups defined in the Australian Standard Classification of Occupations, which ranges from 1 (highest, professionals and managers) to 8 (labourers, clerical, sales, and service workers), with a ninth category for students, home duties, pensioners and the unemployed.[18] Postcodes were dichotomised into 'accessible' area or 'remote' area using the Accessibility/Remoteness Index of Australia (ARIA)[19,20] and used to calculate the Index of Relative Socio-economic Disadvantage (IRSD) scores, which is a marker of socioeconomic status according to residential area.[21] IRSD scores were categorised into quartiles, which is consistent with other studies. Potential confounders obtained from the AEDI data set included Aboriginal and Torres Strait Islander status. We did not adjust for birthweight and gestational age because they are intermediates along the causal pathway and adjusting for these variables could introduce bias.[22,23]

Analysis

Characteristics of mother–infant dyads with and without anaemia of pregnancy were compared using χ^2 tests for categorical variables, independent *t*-tests for continuous variables and Mann–Whitney *U*-test for variables that were not normally distributed.

Perinatal outcomes of women with and without anaemia were compared using generalised linear models with a Gaussian distribution for normally distributed continuous variables and log-Poisson for dichotomous outcomes, with and without adjustment for potential confounders. Complete case analyses were conducted on the sample with the SBR form and all potential confounders.

For the AEDI outcomes, the relative risk associated with anaemia of pregnancy was estimated using generalised linear models with a log-Poisson link, first unadjusted, and then adjusted for potential confounders. Complete case analyses were conducted on the sample with successful linkage of perinatal with AEDI data. Teachers did not complete the AEDI for children they identified as having special needs, and therefore these children had to be excluded from the analysis. Special needs status are children who require special assistance in the classroom due to a chronic medical, physical, or intellectually disabling condition, such as Down's syndrome, autism, and visual or hearing impairments. We explored the association between anaemia and AEDI in sex strata because of differences in cognitive and behavioural outcomes between girls and boys, but because the results were consistent, we present the pooled results.

To minimise non-response bias, missing data on any of the perinatal, AEDI, or confounders were imputed under the assumption that the data were missing at random.[24] Multiple imputation by chained equations was used to impute missing values.[25] Two separate imputation models were established, one for perinatal and another for AEDI outcomes. For perinatal data, the imputation was conducted on all women with a SBR and the model included all sociodemographic characteristics, perinatal outcomes, medical complications during pregnancy, sex, birthweight, and gestational age. For AEDI data, the imputation was conducted on children with ≥1 AEDI domain measured and the model included all AEDI domain scores, exposure, confounders, sex, birthweight, and gestational age. Twenty imputed data sets were generated and the results of imputed analyses were combined using Rubin's rules.[26] The distribution of variables in the imputed data sets was consistent with the complete case data (data not shown). Analyses were conducted using STATA version 12.1.

Results

All individuals with the SBR completed between 1999 and 2005 were included. Figure 1 shows that there were 124 061 mother–infant dyads in the perinatal data set, which formed the final analysis set for perinatal outcomes. There were 17 818 children in the AEDI data set and of these, 14 607 AEDI records were linked to perinatal data. The inability to link is likely due to children with no perinatal record form (~600 South Australians and ~2000 born interstate or overseas), and ~500 with no AEDI record due to emigration out of South Australia.[27] The final data set for the analysis of developmental vulnerability involved 13 654 children.

Sociodemographic characteristics differed between women with and without anaemia of pregnancy (Table 1). Women with anaemia were younger, more likely to be multiparous, Aboriginal, or Torres Strait Islander, have a lower skilled occupation and less likely to have a partner, compared with women without anaemia.

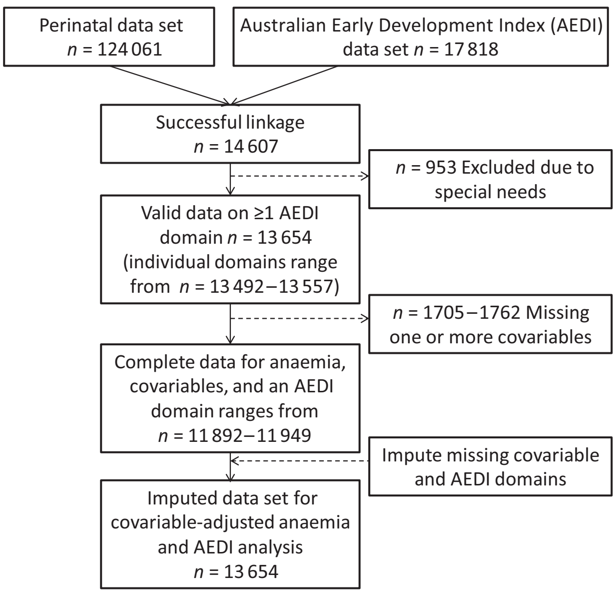

Figure 1. Flow of individuals through the study.

Table 2 shows perinatal outcomes according to anaemia of pregnancy. After adjustment for confounders, the complete case analyses showed that anaemia was associated with a higher risk of fetal distress, higher birthweight, slightly lower gestational age and less resuscitation at birth. The birthweight-for-gestational age z-score indicates that after taking into account gestational age at birth, infants of anaemic mothers had higher birthweight than infants of non-anaemic mothers. *Post hoc* exploratory analyses among infants born full term (37–41 weeks gestation) indicated no difference in the proportion of LBW infants across the groups (anaemia; 155/7620 (2%), no anaemia 2235/105 721 (2%), $P = 0.639$). Results of the imputed analyses were similar, although the effect size was smaller for birthweight and slightly stronger for preterm birth and gestational age.

In unadjusted comparisons, anaemia of pregnancy was associated with developmental vulnerability across all AEDI domains, except emotional maturity (Table 3). However, associations were attenuated after adjustment for confounders. The imputed analyses were consistent in the direction and magnitude of the complete case analyses. *Post hoc* exploratory analyses in which preterm infants were excluded did not differ from the main analyses. For example, anaemia of pregnancy was associated with 1.07 [0.92, 1.24] higher risk of vulnerability on ≥1AEDI domains in adjusted analyses.

Comment

The present study provides evidence that children born to South Australian mothers who were diagnosed with anaemia of pregnancy are not at an elevated risk of developmental problems at school entry. These data show that in the modern Australian context, infants born to women with anaemia have slightly lower gestational ages and more preterm births than infants of non-anaemic women. Because birthweight and gestational age are collinear, we used birthweight-for-gestational age z-scores to examine weight at birth independently of gestational age. This finding is supported by additional analyses showing that among infants born full-term gestation (37–41 weeks), there is no difference in proportion of children born LBW between anaemic and non-anaemic women.

Table 1. Sociodemographic characteristics of all live births 1999–2005 in South Australia and 2009 Australian Early Development Index (AEDI) scores

	All births 1999–2005 (n = 124 061)			Linked to 2009 AEDI (n = 13 654)		
	Anaemia[a] (n = 8764) (%)	No anaemia (n = 115 297) (%)	MD [95% CI] or P	Anaemia (n = 855) (%)	No anaemia (n = 12 799) (%)	MD [95% CI] or P
Maternal age	28.6 ± 6.3	29.7 ± 5.5	1.1 [1.0, 1.2]	29.2 ± 6.2	30.0 ± 5.5	0.7 [0.4, 1.1]
Partnered	6934 (79)	100 378 (87)	<0.001	716 (84)	11 312 (88)	<0.001
Missing	4 (0.05)	20 (0.02)		0 (0)	3 (0.02)	
Smoked during pregnancy	2033 (23)	21 456 (19)	<0.001	149 (17)	2119 (17)	0.773
Missing	306 (4)	3269 (3)		23 (3)	328 (3)	
Maternal ATSI status	649 (7)	2479 (2)	<0.001	60 (7)	230 (2)	<0.001
Nulliparous	3342 (38)	48 340 (42)	<0.001	327 (38)	5498 (43)	<0.001
Singleton	8501 (97)	113 594 (99)	<0.001	833 (97)	12 591 (99)	0.037
Maternal occupation			<0.001			<0.001
1 (highest)	417 (5)	8513 (7)		71 (8)	1082 (8)	
2	714 (8)	12800 (11)		77 (9)	1585 (12)	
3	439 (5)	6442 (6)		32 (4)	706 (6)	
4	221 (3)	3998 (4)		20 (2)	455 (4)	
5	838 (10)	15429 (13)		81 (10)	1758 (14)	
6	1045 (12)	17085 (15)		107 (13)	1951 (15)	
7	55 (1)	797 (1)		7 (1)	75 (1)	
8 (lowest)	312 (3)	4526 (4)		29 (3)	491 (4)	
9 (home duties, students, unemployed)	4316 (49)	42052 (36)		388 (45)	4168 (33)	
Missing	407 (5)	3655 (3)		43 (5)	528 (4)	
Paternal occupation			<0.001			<0.001
1 (highest)	1077 (12)	20068 (17)		118 (14)	2330 (18)	
2	880 (10)	14025 (12)		98 (12)	1624 (13)	
3	369 (4)	5631 (5)		43 (5)	599 (5)	
4	1378 (16)	20743 (18)		115 (14)	2356 (18)	
5	171 (2)	3224 (3)		20 (2)	367 (3)	
6	430 (5)	6355 (6)		33 (4)	719 (6)	
7	513 (6)	7172 (6)		44 (5)	769 (6)	
8 (lowest)	1228 (14)	15696 (14)		125 (15)	1783 (14)	
9 (home duties, students, unemployed)	1339 (15)	11107 (10)		30 (15)	997 (8)	
Missing	1379 (16)	11276 (10)		129 (15)	1255 (10)	
Inter-pregnancy interval						<0.001
No previous pregnancies	3344 (38)	48 357 (42)	<0.001	327 (38)	5498 (43)	
<1 year	308 (4)	3003 (3)		22 (3)	334 (3)	
1 to <3 years	2916 (33)	37 356 (32)		286 (34)	4130 (32)	
>3 years	2108 (24)	25 838 (22)		202 (24)	2687 (21)	
Missing	88 (1)	743 (1)		18 (2)	150 (1)	
Male infant	4322 (49)	59 266 (51)	<0.001	402 (47)	6451 (50)	0.055
IRSD quartiles						<0.001
1 (most disadvantaged)	4215 (48)	40 850 (35)	<0.001	407 (48)	4347 (34)	
2	1761 (20)	26 035 (23)		191 (22)	2810 (22)	
3	1106 (13)	19 328 (17)		104 (12)	2309 (18)	
4 (least disadvantaged)	1661 (19)	28 688 (25)		151 (18)	3301 (26)	
Missing	21 (0.2)	396 (0.3)		3 (0.4)	40 (0.3)	
Living in remote area	338 (4)	4390 (4)	0.896	38 (4)	456 (4)	0.396
Missing	16 (0.2)	234 (0.2)		0 (0)	1 (0.01)	
Number of antenatal visits	10 [8, 12]	11 [9, 12]	<0.001	11 [9, 12]	11 [10, 12]	0.033
Missing	1246 (15)	13 091 (11)		83 (10)	1116 (9)	

[a]Data are reported as mean ± standard deviation, number (percentage) or median (25th to 75th quartiles). The characteristics of women with and without anaemia were compared using χ^2 tests for categorical variables, independent *t*-tests for continuous normally distributed variables and Mann–Whitney *U*-tests for variables that were not normally distributed.

Maternal occupation was calculated according to the Australian Bureau of Statistics methods and grouped into major categories based on education and skill level, where 1 is highest and 5 is lowest.[18] IRSD scores were calculated from postcodes according to the Australian Bureau of Statistics indicator of disadvantaged area.[21] Remoteness was determined according to the Accessibility/Remoteness Index of Australia.[19,20]

ATSI, Aboriginal or Torres Strait Islander; CI, confidence interval; IRSD, Index of Relative Socio-economic Disadvantage, MD, mean difference; P, probability.

Table 2. Anaemia of pregnancy, perinatal and birth outcomes

	Anaemia[a] $n = 8764$	No anaemia[a] $n = 115\,297$	Complete case analyses ($n = 96\,290$) Unadjusted mean difference or IRR [95% CI][b]	Complete case analyses ($n = 96\,290$) Adjusted mean difference or IRR [95% CI][c]	Imputed data sets ($n = 124\,061$) Adjusted mean difference or IRR [95%CI]
Fetal distress	1196 (13.7)	13 649 (11.8)	1.15 [1.09, 1.22]	1.19 [1.10, 1.27]	1.20 [1.13, 1.27]
Birthweight (g)	3327 ± 666	3373 ± 578	−46 [−33, −58]	36 [23, 49]	14 [2, 26]
Low birthweight (<2500 g)	820 (9.4)	7014 (6.1)	1.54 [1.44, 1.65]	0.92 [0.82, 1.02]	1.08 [1.00, 1.16]
Gestational age (week)	38.6 ± 2.4	39.0 ± 1.9	−0.34 [−0.30, −0.38]	−0.05 [−0.09, −0.004]	−0.15 [−0.19, −0.11]
Preterm birth (<37 weeks)	1055 (12.0)	8551 (7.4)	1.62 [1.53, 1.72]	1.14 [1.04, 1.25]	1.23 [1.15, 1.31]
Birthweight-for-gestational age *z*-score	0.05 ± 1.05	−0.02 ± 1.02	0.06 [0.04, 0.09]	0.11 [0.09, 0.14]	0.11 [0.09, 0.14]
Resuscitation at birth			0.94 [0.92, 0.96]	0.91 [0.88, 0.95]	0.94 [0.91, 0.97]
None	4241 (48.4)	51 766 (44.9)			
Aspiration	1443 (16.5)	24 351 (21.2)			
Oxygen	2173 (24.8)	27 898 (24.2)			
IPPV	654 (7.5)	8175 (7.1)			
Other	253 (2.9)	3170 (2.7)			

[a]Data are reported *n* (%) or mean ± standard deviation.
[b]Perinatal outcomes were compared between anaemic and non-anaemic groups using generalised linear models with Gaussian distribution to calculate mean differences in continuous normally distributed outcomes, and log-Poisson models were used to calculate the incident rate ratio (IRR) for dichotomous outcomes. Resuscitation at birth was categorised into a dichotomous outcome (none vs. any) for the analysis of IRR.
[c]Analyses were adjusted for the following potentially confounding variables; singleton/twin, maternal age, smoking in pregnancy, number of antenatal visits, parity, inter-pregnancy interval, maternal occupation, paternal occupation, maternal Aboriginal or Torres Strait Islander status, the Index of Relative Socio-economic Disadvantage and for living in a remote/not remote area.
CI, confidence interval; IPPV, intermittent positive pressure ventilation; IRR, incidence rate ratio.

The 7% prevalence of antenatal anaemia found in our study was substantially lower than estimates from the UK (24%)[28] and from other high-income countries, which range from 12% to 22%.[1,29] The reasons underlying the disparities in anaemia in our study and the UK is not clear as the cut-off values for the diagnosis were the same.[28] The prevalence of anaemia reported here is more accurate than the 12–22% predicted from analytical models.[1,29] Our data are consistent with other high-income countries where there has been national collection of anaemia, including the USA (5.7%) and Switzerland (9.7%).[1]

South Australian practice guidelines recommend that women be tested for anaemia at the first antenatal clinic visit and at 28 weeks.[4] Three quarters of pregnant women attend their first antenatal appointment before 14 weeks gestation.[30] Furthermore, <0.5% of births occur before 28 weeks in this population, and therefore typical pregnancies will involve two tests for anaemia. A diagnosis of anaemia results in a recommendation for iron supplementation;[4] therefore, routine testing and treatment of anaemia at least twice during pregnancy will have reduced fetal exposure to an anaemic environment and may have contributed to the small effects.

A recent systematic review by Haider *et al*. reported that anaemia of pregnancy is associated with lower birthweight and gestational age, and higher risks of preterm birth in cohort studies, and meta-analysis of 12 randomised trials of iron supplements reducing the risk of preterm birth by 14% (relative risk 0.84 [95% CI 0.68, 1.03]).[31] As discussed in the review,[31] the mechanism for an association between anaemia and preterm birth may be due to factors other than iron deficiency, such as stress or hypoxia-induced increase in corticotrophin.[32] This warrants investigation, but we could not explore this further because of a lack of information on the cause of anaemia. The association between anaemia and preterm birth could be biased by more frequent testing of high-risk pregnancies that result in preterm birth, coupled with the increase in haemoglobin (and

Table 3. Anaemia of pregnancy and relative risk of being developmentally vulnerable on the Australian Early Development Index domains[a]

	Complete case			Imputed data sets ($n = 13\,654$)[b]	
	n	IRR	95% CI	IRR	95% CI
Unadjusted analyses					
Physical health and well-being	13 557	1.45	[1.21, 1.73]	1.43	[1.20, 1.72]
Social competence	13 556	1.37	[1.14, 1.64]	1.35	[1.13, 1.62]
Emotional maturity	13 492	1.15	[0.94, 1.40]	1.16	[0.95, 1.41]
Language and cognitive skills	13 528	1.54	[1.23, 1.94]	1.52	[1.21, 1.91]
Communication and general knowledge	13 555	1.58	[1.28, 1.94]	1.57	[1.21, 1.91]
Developmental vulnerability on ≥1 domain	13 505	1.31	[1.16, 1.46]	1.30	[1.16, 1.46]
Adjusted analyses[c]					
Physical health and wellbeing	11 949	1.19	[0.96, 1.48]	1.17	[0.96, 1.43]
Social competence	11 950	1.16	[0.94, 1.44]	1.13	[0.92, 1.38]
Emotional maturity	11 892	1.04	[0.83, 1.30]	0.99	[0.80, 1.22]
Language and cognitive skills	11 929	1.20	[0.92, 1.56]	1.14	[0.89, 1.45]
Communication and general knowledge	11 948	1.26	[0.99, 1.60]	1.23	[0.98, 1.53]
Developmental vulnerability on ≥1 domain	11 906	1.11	[0.95, 1.28]	1.11	[0.96, 1.27]

[a]Developmental vulnerability is defined as being in the lowest 10% of scores on each domain. IRR was calculated using generalised linear models with log-Poisson links.
[b]Children with valid data on at least one AEDI domain were included in the imputed analysis. Multiple imputation using chained equations was used to impute any missing outcome and covariable data. Twenty imputed data sets were created and the association between anaemia of pregnancy and vulnerability on the AEDI was combined using Rubin's rules.[26]
[c]Analyses were adjusted for: singleton/twin, maternal age, smoking in pregnancy, number of antenatal visits, parity, inter-pregnancy interval, maternal occupation, paternal occupation, Aboriginal or Torres Strait Islander status, Index of Relative Socio-economic Disadvantage, and remote/not remote area.
CI, confidence interval; IRR, incident rate ratio.

therefore lower anaemia status) as pregnancy approaches full term,[33,34] although routine screening of anaemia prior to the third trimester will have ameliorated this effect in our study. Treatment of anaemia with iron supplements resulted in small increases to birthweight.[31] This is consistent with our observation of a slightly higher birthweight-for-gestational age *z*-score among infants born to anaemic mothers, many of whom are likely to have taken iron supplements to treat their anaemia. Steer *et al*. has shown that the highest birthweights and lowest risks of being born LBW are associated with haemoglobin concentrations within the range considered anaemic[35,36] and this is supported by other studies.[34,37] While the mechanisms for higher birthweight are not clear, there is speculation that better plasma volume expansion or lower blood viscosity due to lower haemoglobin concentrations might result in better placental perfusion[34,38] and may also explain the reduced need for resuscitation among infants born to anaemic mothers. Together with our data, evidence from high-income countries suggests that associations between anaemia of pregnancy and birthweight are small and probably of little clinical significance.[31,37]

Other literature shows that supplementation of pregnant anaemic women with iron attenuates poor cognitive development of 2-year-old Chinese children.[39] This is consistent with the small effects of anaemia on children's developmental vulnerability in the present study. Even though anaemia was defined by haemoglobin cut-offs, we were unable to corroborate the 1966 Finnish cohort study by Fararouei *et al*. in which haemoglobin measured during the ninth month of gestation was negatively associated with school achievement at 14 years of age and lower odds ratio (OR) of having completed higher education at 31 years (OR = 0.86 [95% CI 0.76, 0.98], $n = 11\,656$).[10] This may be due to differences in study designs, analytical models, or due to improvements in anaemia management and perinatal care over the last 40 years; however, an alternative explanation is that the effects of anaemia may not be evident until later ages when cognitive abilities are fully developed. On the contrary, Lewis *et al*. reported no association between haemoglobin in pregnancy and children's intelligence quotient scores at 8 years regardless of whether haemoglobin was measured early or late in pregnancy, and this was also supported by a Mendelian randomisation study of genes associated with higher maternal haemoglobin.[40]

By utilising government administrative data sets on the entire population of South Australia, we have minimised selection biases. The standard definition of anaemia of pregnancy used in the SBR form and the routine collection of perinatal and developmental data by trained midwives and teachers (respectively) will limit differential misclassification and recall/reporting biases. One of the drawbacks of using a large data set designed for administrative purposes is that we cannot explore whether the severity of anaemia, gestational age or trimester in which anaemia occurred can affect children's developmental vulnerability because this data is not collected. While studies in rodents and non-human primates suggest that neurological outcomes might differ according to which trimester of pregnancy anaemia occurs,[9,41,42] there is a paucity of evidence from human studies, and therefore, this is an important area for future research. We addressed missing covariable information in the data sets by using multiple imputation. The low quantity of missing information and the consistency between the complete case and imputed results, suggest the analyses are robust. The analysis is limited to the confounders that were available in the data sets but as with all observational studies, there is potential for unmeasured or residual confounding. Other confounders that were not available in our data sets (e.g. maternal education), are likely to further attenuate the effect of anaemia on developmental vulnerability and this is the reason why we have taken care to not overstate the small effect estimates. Despite the small effect estimates, it is unlikely that the exposure (anaemia of pregnancy) lacked signal for detecting effects on developmental vulnerability because it was sufficient to detect known associations between anaemia and perinatal outcomes. Another limitation of this study is that we were unable to determine if the association between anaemia and perinatal outcomes or developmental vulnerability differed according to the cause of the anaemia or compliance with treatment, again because these data were not collected.

Our study has important implications for Australia and other high-income countries where iron deficiency is the major cause of anaemia during pregnancy,[3,29] and routine iron supplementation is not practiced. There is some concern that routine iron supplementation may be harmful for iron-replete women[3,6,7,37,38,43] and might cause behavioural problems among children.[44] Iron deficiency anaemia during pregnancy is associated with a higher risk of iron deficiency in infancy,[45] which increases the pressure for routine iron supplementation to protect against future deficiency. Given that we have been unable to demonstrate a long-term effect of anaemia in pregnancy on children's developmental vulnerability, the data from this study supports a cautious approach to routine supplementation – at least until evidence to the contrary becomes available.

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