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## RESEARCH ARTICLE

# Maternal haemoglobin in pregnancy and offspring childhood weight and height trajectories: analysis of a prospective birth cohort study [version 1; peer review: 1 approved with reservations]

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## Abstract

**Background:** Both anaemia and high haemoglobin in pregnancy are associated with adverse pregnancy outcomes including foetal growth restriction. The objective of this study was to investigate the associations between maternal haemoglobin in pregnancy and trajectories of length/height and weight from birth through childhood.

**Methods:** Data from 7,597 singleton pregnancies in the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing, prospective, UK population-based pregnancy cohort study were used. We examined associations between maternal haemoglobin (overall pregnancy and trimester specific) and offspring length and weight at birth, as well as trajectories of height and weight gain from birth to age 10 years derived from multilevel models.

**Results:** Mean pregnancy haemoglobin was 11.61 g/dL (SD 1.12). For each 1g/dL higher mean overall pregnancy haemoglobin, offspring were on average -0.30 cm shorter (95%CI: -0.35, -0.24, p <0.001), and -97.7 g lighter (95%CI: -110.42, -84.93, p <0.001) at birth when adjusting for potential confounders. Trimester specific inverse associations with birth length and weight were strongest for third trimester haemoglobin. There was evidence of a positive association between maternal haemoglobin levels and offspring height gain up to the age of one year and no strong evidence of associations between pregnancy haemoglobin and childhood weight gain.

**Conclusions:** In high income countries, higher maternal haemoglobin in pregnancy may be a concern, as well as anaemia. Further studies are needed to define 'high' haemoglobin in pregnancy and whether

## Open Peer Review

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1

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1. **Tom Norris** , Loughborough University, Loughborough, UK

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monitoring of women with high pregnancy haemoglobin is warranted.

### Keywords

ALSPAC, maternal health, anaemia, growth, haemoglobin, pregnancy



This article is included in the [Avon Longitudinal Study of Parents and Children \(ALSPAC\)](#) gateway.

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## Introduction

The estimated prevalence of anaemia among pregnant women is around 38% worldwide<sup>1</sup> and is considered to be a 'moderate' public health problem by the World Health Organisation (WHO)<sup>2</sup>. In the UK, anaemia, most commonly reflecting iron deficiency anaemia (IDA)<sup>3</sup> affects some 15% of pregnancies.

There is evidence that maternal anaemia in pregnancy is associated with adverse pregnancy outcomes including low birthweight, increased risk of pre-term delivery<sup>4-6</sup>, small-for-gestational-age babies, perinatal IDA<sup>7</sup> and foetal distress<sup>8</sup> and stillbirth<sup>9,10</sup>. Furthermore, while infants born at term at a normal birth weight have adequate iron stores for the first few months of life<sup>11</sup>, it has been shown that infants of mothers who have low iron stores in pregnancy are more likely to develop anaemia<sup>7,12</sup>. While most recent research has focussed on the potential adverse effects of low haemoglobin in pregnancy, there is also evidence that higher levels of haemoglobin, haematocrit, and ferritin are associated with poor pregnancy outcomes including stillbirth, foetal growth restriction, pre-term delivery, and preeclampsia<sup>4,5,13-19</sup>.

To the best of our knowledge, the association of maternal haemoglobin during pregnancy with offspring growth in childhood has not previously been studied. In this study, we examine the associations of maternal haemoglobin in pregnancy with offspring length and weight at birth, and subsequent growth up to the age of 10 years using data from a large, population based prospective pregnancy cohort in a high-income country setting.

## Methods

### Ethical statement

Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees (project approval number B1107). Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time (listed at <http://www.bristol.ac.uk/alspac/researchers/research-ethics/>).

### Study population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is an ongoing, prospective, population-based, pregnancy cohort study. Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study. The initial number of pregnancies enrolled was 14,541. Of these pregnancies, 14,273 singleton pregnancies were followed up resulting in 13,617 singleton live born offspring who survived to at least one year of age. 7,957 of these mother-child pairs had complete data included in our analysis. Further details of this cohort study have been described in detail previously<sup>20,21</sup>. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool at: <http://www.bristol.ac.uk/alspac/researchers/our-data/>. Figure 1 shows the participants flow-chart for the present study.

### Maternal haemoglobin in pregnancy

Values of all routinely measured haemoglobin in pregnancy (in g/dL) were extracted from antenatal medical records. Women had between one and 20 haemoglobin measurements with a mode of three measurements (mean 3.36) across the pregnancy. Mean haemoglobin values were calculated for each woman with more than one measurement across: i) the entire pregnancy; and ii) for each trimester. Trimesters were defined as: first trimester (<13 completed weeks of gestation), second ( $\geq$ 13 weeks to <26 weeks) and third ( $\geq$ 26 weeks).

### Offspring length and weight at birth and during childhood

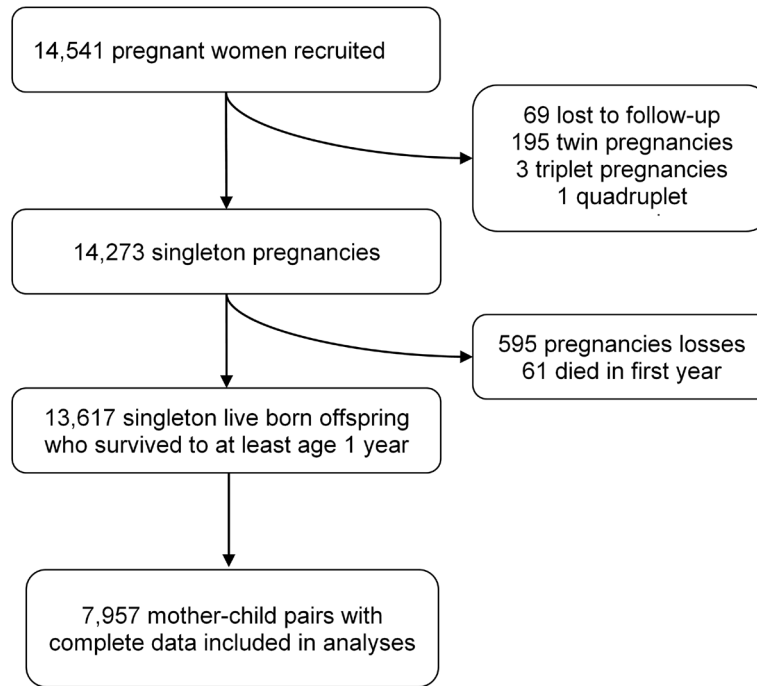
Birth length (crown to heel length) was measured by ALSPAC staff who visited newborns soon after birth (median 1 day, range 1–14 days) using a Harpenden neonatometer (Holtain Ltd)<sup>22</sup>. Subsequent height data for the children were obtained from health visitor records, parental reports and measurements taken at clinic visits, as previously described<sup>23</sup>. Birth weight was extracted from medical records and up to four further weight measurements were taken from routine health visitor records (as part of standard UK childcare) at around two, 10, 21 and 48 months. Additionally, mothers were asked to report their child's height and weight regularly from three years, and clinics were carried out at seven, eight, nine, and 10 years for all participants and at four, eight, 12 and 18 months for a subset of 10% of participants. Height and weight measures that were self-reported by parents were coded with a 'self-report' flag. Previous research has demonstrated that the accuracy of measurements varies between clinical and parent-reported measurements but that measurements from research clinics and routine child healthcare records have similar accuracy<sup>23,24</sup>.

### Other measures

Maternal age (in years) at the start of the pregnancy, maternal ethnicity (as a binary variable - white, non-white), parity (as a binary variable describing  $\leq$ 2 pregnancies including the study pregnancy or >2 pregnancies), and maternal height were all obtained from self-reported questionnaires completed by the mother. Maternal pre-pregnancy body mass index (BMI) was derived from pre-pregnancy weight self-reported by the mother and their self-reported height. Maternal smoking in pregnancy, categorised as "None", "Temporary" and "Through-out", was based on self-report. Household social class was allocated using the highest parental occupation as self-reported by the mother according to the 1991 British Office of Population and Census Statistics (OPCS) classification. Offspring gender (as a binary variable) was obtained from medical records. Gestational age at delivery was based on last menstrual period (LMP) when the mother was certain of this, for uncertain LMPs and conflicts with clinical assessment the ultrasound assessment was used. Where maternal report and ultrasound assessment conflicted, an experienced obstetrician reviewed clinical records and made a best estimate.

### Statistical analysis

Offspring growth trajectories were previously estimated using multilevel linear spline models<sup>25</sup>. Multilevel models permit



**Figure 1. Inclusion/exclusion flowchart.**

individual variation in growth trajectories with random effects allowing each individual participant to have person-specific intercepts and slopes. Models had two levels, with measurement occasions at level 1 nested within individuals at level 2. Knot points were placed at three months, one year, three years and 10 years for height and three months, one year, seven years and 10 years for weight; with linear changes in growth assumed between these ages, as previously described<sup>25</sup>.

Here, we ran spline models including maternal pregnancy haemoglobin (overall pregnancy mean, trimester specific mean) as an independent variable in both unadjusted and a confounder adjusted models. We considered the following to be potential confounders: source of height/weight measurement, gender, maternal age, pre-pregnancy BMI and height, length of gestation, ethnicity, maternal pregnancy smoking status, parity, and household social class. To ensure comparability between unadjusted and adjusted models, only those pregnancies with all available covariables were considered in the unadjusted model as well as in the adjusted model.

We tested for departure from a linear relationship between maternal overall pregnancy haemoglobin and offspring growth by comparing a model in which quintiles of maternal haemoglobin was entered as a continuous versus four dummy variables.

Participants included in our analysis were compared with participants of the ALSPAC cohort who were excluded from our analysis due to missing data. We compared them in terms of household social class, maternal height, weight,

ethnicity, smoking status and age, and pregnancy gestation length, parity and mean Hb using t-tests to compare means for continuous data and chi<sup>2</sup>-tests to compare frequency distributions as appropriate.

Data were analysed using Stata Version 13 (StataCorp, College Station, TX, USA) with the MLwiN (version 2.36) multilevel modelling plug-in tool 'runmlwin'<sup>26</sup>.

## Results

A total of 7957 singleton pregnancies were included in the analyses of overall pregnancy mean haemoglobin. [Figure 1](#) shows the participant flow chart. Mean overall pregnancy haemoglobin was 11.61 g/dL (SD 1.12). Trimester specific means were: 12.53 g/dL (SD 0.89; N=5786) for the first trimester, 11.90 g/dL (SD 1.04, N=2011) for the second, and 11.28 g/dL (SD 0.86, N=7512) for the third.

Mothers excluded from analyses due to missing data were shorter, more likely to smoke in pregnancy, to be of non-white ethnic origin, to be multiparous and to deliver prematurely. Finally, mean pregnancy haemoglobin in excluded pregnancies was lower in excluded women, but only marginally ([Table 1](#)).

There was no evidence for departure from a linear relationship between maternal pregnancy haemoglobin and offspring outcomes.

## Height

For each 1g/dL higher mean overall pregnancy haemoglobin, offspring were on average 0.30 cm shorter at birth

**Table 1. Characteristics of mothers included and excluded from analyses.**

	Participants included in our analysis		Participants excluded from our analysis		p-value
	No.	%	No.	%	
<b>Gender</b>	<b>7957</b>		<b>5565</b>		0.10
Female	3900	49.0	2647	33.3	
<b>Ethnicity</b>	<b>7957</b>		<b>3998</b>		<0.01
Non-white	135	1.7	173	4.3	
<b>Household social class</b>	<b>7957</b>		<b>1285</b>		<0.01
i	1235	15.5	144	11.2	
ii	3597	45.2	546	42.5	
iiinm	2183	27.4	370	28.8	
iiim	700	8.8	175	13.6	
iv/v	242	3.0	50	3.9	
<b>Maternal smoking during pregnancy</b>	<b>7957</b>		<b>4738</b>		<0.01
Never	6367	80.0	3095	65.3	
Temporary/Some	459	5.8	419	8.8	
Throughout	1131	14.2	1224	25.8	
<b>Parity</b>	<b>7957</b>		<b>4785</b>		<0.01
≤2 pregnancies	7658	96.2	4345	90.8	
	<b>No.</b>	<b>Mean (SD)</b>	<b>No.</b>	<b>Mean (SD)</b>	
Maternal height (cm)	7957	164.21 (6.66)	3894	163.43 (6.84)	<0.01
Maternal BMI (kg/m <sup>2</sup> )	7957	22.91 (3.72)	3239	23.02 (4.19)	0.19
Maternal age (years)	7957	28.68 (4.58)	5565	26.94 (5.33)	<0.01
Gestation (weeks)	7957	39.54 (1.68)	5565	39.39 (2.04)	<0.01
Mean pregnancy Hb (g/dL)	7957	11.72 (0.80)	4891	11.61 (0.87)	<0.01

BMI, body mass index; Hb, haemoglobin; SD, standard deviation.

(95%CI -0.35, -0.24,  $p < 0.001$ ), when adjusting for potential confounders (Table 2). Maternal overall pregnancy haemoglobin was positively associated with offspring linear growth between the ages of 0-3 months and 3-12 months in both the unadjusted and adjusted models, so that differences in birth length did not persist beyond the age of 12 months. There was no strong evidence of associations with growth beyond the first year. Similar associations were noted when each trimester was analysed separately, with the largest association with birth length observed for trimester 3 (mean difference in birth length -0.36 cm; 95%CI: -0.41, -0.30; Table 3).

### Weight

For each 1g/dL higher mean overall pregnancy haemoglobin, offspring were on average -97.7g lighter at birth (95% CI -110.42g to -84.93g,  $p < 0.001$ ), when adjusting for potential confounders (Table 4). Overall pregnancy haemoglobin was positively associated with offspring weight gain between the ages of 3-12 months and 7-10 years in the unadjusted model ( $p < 0.001$ ), but in the adjusted model only the association with weight gain between 3-12 months remained. By the age of 12 months the mean difference was less than 40g (calculated by summing the effect estimates for birth weight and

**Table 2. Associations between mean overall pregnancy haemoglobin (g/dL) and birth length and height change.**

N = 7957	Model 1			Model 2		
	Mean diff.	95% CI	p value	Mean diff.	95% CI	p value
<b>Birth length difference (cm)</b>	-0.22	(-0.27, -0.16)	<0.001	-0.30	(-0.36, -0.24)	<0.001
<b>Change in height from 0-3 months (cm/year)</b>	0.25	(0.04, 0.46)	0.02	0.25	(0.001, 0.51)	0.05
<b>Change in height from 3-12 months (cm/year)</b>	0.24	(0.09, 0.39)	0.002	0.17	(-0.01, 0.35)	0.07
<b>Change in height from 1-3 years (cm/year)</b>	0.003	(-0.04, 0.05)	0.86	-0.01	(-0.06, 0.05)	0.84
<b>Change in height from 3-10 years (cm/year)</b>	0.02	(0.01, 0.04)	0.01	0.01	(-0.01, 0.03)	0.57

Model 1 – unadjusted.

Model 2 – adjusted for confounders; source of measurement, gender, maternal BMI, maternal height, maternal age, gestational age at delivery, ethnicity, maternal pregnancy smoking status, parity, household social class.

BMI, body mass index; CI, confidence interval.

**Table 3. Trimester specific associations between maternal pregnancy haemoglobin (g/dL) and birth length and height gain\*.**

	1 <sup>st</sup> trimester			2 <sup>nd</sup> trimester			3 <sup>rd</sup> trimester		
	N = 5786			N = 2011			N = 7512		
	Mean diff.	95% CI	p value	Mean diff.	95% CI	p value	Mean diff.	95% CI	p value
<b>Birth length (cm)</b>	-0.07	(-0.13, 0.003)	0.04	-0.15	(-0.23, -0.06)	<0.001	-0.36	(-0.41, -0.30)	<0.001
<b>Height gain from 0-3 months (cm/year)</b>	0.07	(-0.21, 0.34)	0.63	0.15	(-0.25, 0.54)	0.47	0.28	(0.04, 0.53)	0.02
<b>Height gain from 3-12 months (cm/year)</b>	-0.03	(-0.22, 0.16)	0.76	-0.05	(-0.35, 0.25)	0.75	0.24	(0.07, 0.42)	0.01
<b>Height gain from 1-3 years (cm/year)</b>	0.03	(-0.02, 0.09)	0.23	0.06	(-0.02, 0.14)	0.16	-0.02	(-0.07, 0.03)	0.52
<b>Height gain from 3-10 years (cm/year)</b>	0.003	(-0.02, 0.02)	0.82	-0.03	(-0.06, 0.003)	0.08	0.01	(-0.01, 0.03)	0.33

\* Results are from the confounder adjusted model that includes: source of measurement, gender, maternal BMI, maternal height, maternal age, gestation, ethnicity, maternal pregnancy smoking status, parity, household social class.

BMI, body mass index; CI, confidence interval.

weight gain 0–3 and 2–12 months). When we examined each trimester separately (Table 5), mean maternal haemoglobin in each trimester was negatively associated with birth weight; the largest effect was observed for the third trimester: for each 1g/dL higher haemoglobin, offspring were on average -112.0 g lighter at birth (95% CI -124.27g to -99.68g,  $p < 0.001$ ), when adjusting for potential confounders.

#### Sensitivity analyses

In analyses excluding all women with mean pregnancy haemoglobin >2 standard deviations away from the mean

(outside 10.07 to 13.3 g/dL), results for both height and weight were largely unchanged, suggesting that associations are not driven by extreme values of pregnancy haemoglobin.

We repeated analyses using multiple linear regression using observed birth length and weight data (as opposed to predicted values from the multilevel model used in the main analysis). These showed similar associations to the main results: a 1g/dL increase in mean haemoglobin was associated with a 0.31 cm lower birth length (95%CI -0.37 to -0.25cm,  $p < 0.001$ ; N=6196 pregnancies) and a 101g lower birth weight (95%CI -114

**Table 4.** Associations between mean overall pregnancy haemoglobin (g/dL) and birth weight and childhood weight gain.

N = 7954	Model 1			Model 2		
	Mean diff.	95% CI	p value	Mean diff.	95% CI	p value
Birth weight (g)	-68.04	(-79.80, -56.27)	<0.001	-97.67	(-110.42, -84.93)	<0.001
Weight gain from 0–3 months (g/year)	47.07	(-13.81, 107.94)	0.13	39.32	(-32.58, 111.23)	0.28
Weight gain from 3–12 months (g/year)	91.35	(46.26, 136.44)	<0.001	66.79	(11.35, 122.23)	0.02
Weight gain from 1–7 years (g/year)	5.41	(-6.85, 17.68)	0.39	-9.57	(-24.42, 5.28)	0.21
Weight gain from 7–10 years (g/year)	102.14	(50.87, 153.40)	<0.001	25.69	(-32.67, 84.05)	0.86

Model 1 – unadjusted.

Model 2 – adjusted for confounders: source of measurement, gender, maternal BMI, maternal height, maternal age, gestational age at delivery, ethnicity, maternal pregnancy smoking status, parity, household social class.

BMI, body mass index; CI, confidence interval.

**Table 5.** Trimester specific associations between maternal pregnancy haemoglobin (g/dL) and birth length and childhood height gain\*.

	Change of 1g/dL mean Hb in first trimester			Change of 1g/dL mean Hb in second trimester			Change of 1g/dL mean Hb in third trimester		
	N = 5784			N = 2011			N = 7510		
	Change	95% CI	p value	Change	95% CI	p value	Change	95% CI	p value
Change in birth weight (g)	-22.56	(-36.37, -8.76)	0.001	-45.86	(-65.52, -26.19)	<0.001	-111.97	(-124.27, -99.68)	<0.001
Change in weight from 0–3 months (g/year)	-64.51	(-141.63, 12.61)	0.10	-71.39	(-180.40, 37.63)	0.20	68.07	(-1.40, 137.55)	0.06
Change in weight from 3–12 months (g/year)	60.75	(1.36, 120.14)	0.05	50.17	(-35.05, 135.40)	0.25	55.78	(2.24, 109.32)	0.04
Change in weight from 1–7 years (g/year)	-5.01	(-20.76, 10.75)	0.53	-19.14	(-41.71, 3.43)	0.10	-5.41	(-19.86, 9.05)	0.46
Change in weight from 7–10 years (g/year)	12.21	(-50.31, 74.74)	0.70	-82.24	(-172.27, 7.79)	0.07	27.03	(-29.79, 83.85)	0.35

\* Results are from the confounder adjusted model that includes: source of measurement, gender, maternal BMI, maternal height, maternal age, gestation, ethnicity, maternal pregnancy smoking status, parity, household social class.

BMI, body mass index; CI, confidence interval; Hb, haemoglobin.

to -88g,  $p < 0.001$ ;  $N = 6092$  pregnancies) when adjusted for confounders. Finally, results did not substantially change when analyses were restricted to mother-offspring pairs with haemoglobin measures in all three trimesters ( $N = 507$ ).

## Discussion

In this study, we found that both overall and trimester specific mean maternal pregnancy haemoglobin were inversely associated with offspring birth length and weight in a



general population sample of British women. These associations were most pronounced for haemoglobin in the third trimester compared to the first and second trimester. However, these differences did not persist into childhood.

Our results for birth weight and length are in line with several reports based on large samples from international studies. A large (n= 153,602) UK retrospective cohort study found that the heaviest babies were born to women with lower haemoglobin: 85 to 95 g/dL when compared to other haemoglobin bands from  $\leq 85$  through to  $>145$ <sup>13</sup>. Another UK study found that both low (defined as  $<10.4$  g/dL) and high haemoglobin ( $>13.2$  g/dL) in early pregnancy were associated with adverse pregnancy outcomes including perinatal death, preterm delivery, and low birthweight<sup>14</sup>. Studies in the US have shown that higher pregnancy haemoglobin is associated with adverse outcomes such as foetal growth retardation<sup>15</sup> and small-for-gestational-age babies<sup>16</sup>. Additionally, a large (n=10,340 women) Chinese study found that a low ( $<130$ g/dL) second trimester haemoglobin, when coupled with a high ( $>130$  g/dL) haemoglobin in the third trimester increased the risk of preterm birth<sup>27</sup>. Finally, in the Generation R study, elevated haemoglobin levels ( $\geq 13.2$  g/dl) were associated with foetal head circumference, length, and weight growth restriction from the third trimester onwards, as well as low birth weight and small-for-gestational-age babies, and hypertensive disorders of pregnancy and preterm delivery<sup>28</sup>.

Despite this evidence, there is a focus on the potential adverse effects of lower pregnancy haemoglobin levels and on assessing the benefits of supplementation<sup>29-32</sup>. The rationale for this in low- and middle-income countries (LMICs) where undernutrition is highly prevalent is understandable, but in high income countries, our own and other results suggest that it is higher haemoglobin that is associated with suboptimal foetal growth.

Maternal blood volume increases by approximately 1.5 litres during pregnancy<sup>33</sup> and red cell mass also increases but to a lesser degree compared to the increase in plasma volume, resulting in a dilutional anaemia<sup>34</sup>. It has been previously posited that this drop in blood osmolality in pregnancy due to plasma dilution would result in reduced blood viscosity; this in turn enhances blood flow in the low pressure intervillous space and thus promotes foetal growth<sup>18</sup>. Conversely, a pathological lack of plasma dilution during pregnancy might result in poorer foetal growth. Therefore, in well-nourished populations, higher maternal haemoglobin levels in pregnancy may reflect impaired haemodilution resulting in reduced foetal growth. An alternative explanation may be that larger fetuses place greater demands on maternal resources, potentially causing lower maternal haemoglobin.

There is no consensus as to threshold values for normal (and thus abnormal) haemoglobin across the different stages of pregnancy. The World Health Organisation<sup>1</sup> defines anaemia in pregnancy to be  $<11.0$  g/dL and accounts for smoking and altitude when providing prevalence estimates but it does not define an upper limit of normal haemoglobin in pregnancy. UK National Institute for Clinical and Health Excellence (NICE)<sup>35</sup> also considers a pregnancy haemoglobin value  $<11.0$  g/dL to be abnormal 'at first contact', and lowers the threshold to

$<10.5$  g/dL at 28 weeks gestation, but no upper normal values are specified. A review of publications of laboratory values in pregnancy found five studies that provided normal haemoglobin reference ranges (2.5 percentile to 97.5 percentile). These were 11.6-13.9 g/dL in first trimester, 9.7-14.8 g/dL in second trimester and 9.5-15.0 g/dL in third trimester<sup>36</sup>.

Future studies of haemoglobin and other iron indices in pregnancy and their relation to pregnancy outcomes in high income settings could be useful in establishing whether maternal haemoglobin, which is routinely measured, may be an inexpensive and useful biomarker for detecting pregnancies at risk for suboptimal foetal growth that may benefit from further assessment.

Our study has both strengths and limitations. Strengths include its prospective design, large sample size, the availability of multiple measures of both haemoglobin across pregnancy and of offspring height and weight as well as data on multiple potential confounders. However, we did not have data on other indices of iron deficiency such as ferritin and haematocrit that would have enabled better characterisation of anaemia by type. Moreover, information on haematinics would have allowed us to examine the ratio of the red blood cell volume to plasma volume to assess and account for physiological plasma dilution.

In conclusion, higher maternal pregnancy haemoglobin is associated with lower offspring birth length and weight of the infant; but these differences do not persist across childhood. High maternal haemoglobin in pregnancy may be a biomarker of impaired haemodilution. Further studies examining the predictive value of maternal pregnancy haemoglobin in relation to foetal growth restriction are warranted.

## Data availability

ALSPAC encourage data sharing to maximise use of the resource, so the executive may put researchers in touch with other groups working in the same area. Most of the data are available for use on request and for these data that are not considered of overlap. The identical dataset for this project can be obtained with the unique project approval number: B1107.

ALSPAC data access is through a system of managed open access. The steps below highlight how to apply for access to the data included in this data note and all other ALSPAC data:

1. Please read the ALSPAC access policy ([http://www.bristol.ac.uk/media-library/sites/alspac/documents/researchers/data-access/ALSPAC\\_Access\\_Policy.pdf](http://www.bristol.ac.uk/media-library/sites/alspac/documents/researchers/data-access/ALSPAC_Access_Policy.pdf)) which describes the process of accessing the data and samples in detail, and outlines the costs associated with doing so.
2. You may also find it useful to browse our fully searchable research proposals database (<https://proposals.epi.bristol.ac.uk/?q=proposalSummaries>), which lists all research projects that have been approved since April 2011.
3. Please submit your research proposal (<https://proposals.epi.bristol.ac.uk/>) for consideration by the ALSPAC Executive Committee. You will receive a response within 10 working days to advise you whether your proposal has been approved.

If you have any questions about accessing data, please email [alspac-data@bristol.ac.uk](mailto:alspac-data@bristol.ac.uk).

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# Open Peer Review

Current Peer Review Status: ?

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## Version 1

Reviewer Report 19 October 2020

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? **Tom Norris** 

School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK

I enjoyed reading the manuscript, which documents the association between maternal haemoglobin during pregnancy and growth in infancy and childhood.

The authors investigated continuous Hb levels across gestation and the association with weight and length at birth and then subsequent growth trajectories across infancy and childhood (up to 10 years). They observed an inverse association between Hb levels and size at birth, such that higher Hb levels were associated with a smaller birth length and lower birth weight. Thereafter, they observed an increased growth rate in length between 0-3 months and 3-12 months and weight change between 3-12 months. However, the strength of evidence for the association between Hb levels and growth, both linear and weight growth, was weak.

I have more specific comments below, split into the sections in which they apply.

### Methods:

- Study population (page 3): Did all dyads have to have all three Hb.
- Maternal haemoglobin in pregnancy (page 3): The authors state that the range of Hb measurements in the sample was 1-20 and I was wondering if the authors had considered the reasons why a woman would need such a high amount of Hb measurements. Does this increased surveillance signify a higher risk pregnancy, which should be acknowledged accordingly. I believe current UK guidelines are for two Hb measurements over the course of pregnancy, so the fact that a lot of women in the sample have had some increased surveillance, the reasons for which and their implications on representativeness should be considered.
- Offspring weight and length data (page 3): The authors acknowledge that there is varying accuracy in measurements taken in different settings and if measured vs self-report. However, did they incorporate this into the growth models, i.e. did they model the level-1 error according to whether data were measured vs self report?

- Can the authors provide a breakdown of the sweeps and the number of participants attending each sweep as a supplementary table. This can help identify whether the chosen growth model is suitable for the data and the number of sweeps (i.e. not overfitting).
- Other measures (page 3): 'sex' and not 'gender'?
- Statistical analysis (page 4): How were knot points chosen (both number and location)?
- What was the variance/covariance structure assumed to be, e.g. covar between birth measurements and measurements in infancy?
- I am not sure about the use of the term confounders for some of these variables. For example, using the traditional definition of confounder, does source of measurement predict both maternal Hb and growth? The same can be asked of offspring gender, length of gestation, parity and perhaps some of the others? If however, these have been identified as confounders because they close the backdoor path between Hb and growth, then I think this should be documented and a DAG presented.

**Results (page 4):**

- The second trimester sample size was much smaller than the first and third? Is this because routine testing is generally in first and third trimesters in UK? Is the sample therefore including a high proportion of women deemed at 'higher risk' (i.e., as they have more intensive monitoring in pregnancy?). It appears the 3rd trimester Hb data is based on a much larger sample than even the first, which is surprising? Do the authors have any suggestion as to why this might be?
- Table 1 (page 5): can the authors provide a footnote for social class levels
- Height and weight associations (page 5 and tables 2 and 4): In general I think the strength of evidence is not particularly strong for the association between Hb levels and growth in both length and weight and I think this should be emphasised in the results and discussion.
- Weight (page 5): I know gestational age is included in the model as a confounder, but given that this is likely not a confounder in the true meaning of the word, did the authors consider using a birth weight outcome variable which was inherently adjusted for gest age, i.e., bwt z-score? This may well complicate the analysis though, as the infant/child outcomes are on the raw scale, not z-scores.
- Tables 2,3: There are instances where the number of decimal places is not consistent in the confidence intervals and I think this may have been done to illustrate that the intervals are not including the null. I think the number of decimal places should be the same throughout. Additionally can the authors please check the CI and p-value for the estimate for birth length in table 3 as the CIs straddle the null but the accompanying p-value doesn't reflect this?

**Is the work clearly and accurately presented and does it cite the current literature?**

Yes

**Is the study design appropriate and is the work technically sound?**

Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**

Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**

Partly

**Are all the source data underlying the results available to ensure full reproducibility?**

Yes

**Are the conclusions drawn adequately supported by the results?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Life course epidemiology, longitudinal analyses

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

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