# Association between maternal hemoglobin concentration and educational attainment in mid-childhood in a high-resource obstetric setting: a prospective cohort study

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## Conflict of Interest

GS acknowledges the support of GE (provided two ultrasound systems for the POP study) and Roche Diagnostics Ltd (provided equipment and consumable for the analysis of PAPP-A, AFP and sFlt1:PLGF). Outside the area of this work, GS has received research support from Roche Diagnostics Ltd, GSK, Illumina and Sera Prognostics (fetal growth restriction, preeclampsia and preterm birth). GS's department has received payment from Roche for a talk given by GS (fetal growth restriction). GS has been a paid consultant to GSK (preterm birth) and is a member of a Data Monitoring Committee for GSK. The other authors have no conflicts of interest including financial interests, activities, relationships, and affiliations to declare.

## Funding

This research was funded by the National Institute for Health and Care Research (NIHR) Cambridge Biomedical Research Centre (Women's Health theme, BRC-1215-20014), an Action Medical Research grant (GN2788) to CEA, GE and Roche Diagnostics Limited. The study was supported by the NIHR Cambridge Clinical Research Facility. The views expressed are those of the author(s) and not necessarily

those of the NIHR or the Department of Health and Social Care. The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. 

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**Word count abstract: 271**

**Word count main document: 2541**

## Condensation page

## Tweetable statement

Maternal anemia in late pregnancy is associated with a 40% higher risk of offspring not attaining the expected educational standards aged 5, but not in later ages in mid-childhood.

## Short title

**Maternal hemoglobin levels and childhood academic outcomes**

## AJOG at a Glance

### Why was this study conducted?

- Despite the common association of maternal Hb levels with perinatal outcomes, their link to childhood neurodevelopment remains uncertain.
- This study aimed to explore the associations between maternal hemoglobin concentrations in early and late pregnancy and educational performance in children aged 5-7 within a well-characterized prospective cohort.

### Key findings

- In this prospective cohort study with data linkage involving >3200 children, maternal anemia in late pregnancy is associated with a 40% higher risk of

offspring not attaining the expected educational standards aged 5, but not in later ages.

- Maternal Hb levels in early pregnancy and changes between 12-28 weeks were not significantly associated with childhood educational outcomes.

**What does this add to what is known?**

- In high-resource settings, enacting a proactive strategy to increase maternal Hb levels is unlikely to substantially affect long-term educational attainment of the offspring.

## Abstract

### Background

Although maternal Hb levels during pregnancy are commonly associated with perinatal outcomes, their link to childhood neurodevelopment remains uncertain.

### Objective

This study aimed to examine the associations between maternal hemoglobin (Hb) in early and late pregnancy with offspring mid-childhood educational attainment in a high-resource obstetric setting.

### Study Design

Pregnancy data from a prospective birth cohort (Pregnancy Outcome Prediction Study, Cambridge, UK, 2008-2012, N=3285) were linked to mid-childhood educational outcomes (Department for Education, UK). Regression models adjusted for maternal, child, and socioeconomic factors were used to determine associations between maternal Hb, pregnancy complications, and offspring educational outcomes (ages 5-7).

### Results

No association was observed between maternal Hb at 12 weeks and the likelihood of either adverse pregnancy outcomes or children meeting expected educational

standards between ages 5-7. Higher maternal Hb at 28 weeks was associated with an increased risk of small-for-gestational age infants (aOR1.26, 95%CI 1.11-1.59; p=0.002) and preterm birth (aOR1.38, 95%CI 1.11-1.81; p=0.005). There were no adverse birth outcomes associated with anemia. However children of mothers who were anaemic at 28 weeks had ~40% increased risk of not attaining expected educational standards at age 5 (aOR1.42, 95%CI 1.03-1.95; p=0.03). There was no association between maternal anemia at 28 weeks and educational performance at ages 6-7. No associations were found between high maternal Hb concentrations (top decile) or change Hb concentrations between 12-28 weeks and childhood educational attainment.

**Conclusions**

Maternal anemia at 28 weeks of pregnancy is associated with reduced educational attainment aged 5, but not at older ages (6-7 years). A proactive approach to increasing maternal hemoglobin in high-resource settings is unlikely to impact on long-term childhood educational attainment.

**Keywords**

Maternal hemoglobin levels, maternal anemia, childhood educational attainment, school performance

## Introduction

40% of pregnant women globally are anemic, making anemia the most common pregnancy complication worldwide[1]. Even in high-resource obstetric settings, maternal hemoglobin (Hb) concentrations below the WHO definition during pregnancy (<110 g/L)[2] are prevalent. Both low[3,4] and high[5–7] maternal Hb concentrations during pregnancy pose risks, suggesting a U-shaped association between maternal Hb and adverse pregnancy and birth outcomes, although this is not universally observed[8].

The relationship between maternal oxygen-carrying capacity, measured Hb concentration across gestation, and fetal neurodevelopment remains unclear. Pregnancy-induced physiological changes, including plasma volume expansion surpassing red cell mass increase, complicate the accurate reflection of maternal oxygen-carrying capacity in Hb concentrations, especially later in pregnancy. Therefore, low Hb levels could signify either reduced oxygen-carrying capacity, potentially impacting fetal neurodevelopment, or a dilutional effect without the same effect. Similarly, elevated Hb levels later in pregnancy may result from inadequate plasma volume expansion, more common in women with placental insufficiency[9], increasing the risk of adverse pregnancy outcomes and potentially impacting their children's neurodevelopment[10]. In view of this uncertainty, a recent systematic review identified the testing of a U-shaped association between maternal Hb and long-term outcomes, including childhood neurodevelopment, as an important knowledge gap[15].

Recent guidance in high-resource obstetric settings advises a pro-active approach to preventing maternal anemia through iron supplementation[16], but the relationship between anemia and childhood neurodevelopment remains unclear. We take a pragmatic approach to this question, by employing nationally-standardized metrics of

expected educational attainment to detect differences in childhood neurodevelopment. We aimed to investigate the associations between maternal hemoglobin concentrations in early and late pregnancy with childhood educational performance at ages 5-7 in a large, well-characterized prospective cohort.

## Material and Methods

### *Study population and data sources*

The Pregnancy Outcome Prediction Study (POPS) is a large prospective birth cohort recruited from a single maternity unit, Rosie Hospital, Cambridge, UK, from 2008-2012. Detailed information about the cohort's design and demographics has been previously described[18,19]. The study enrolled 4,212 nulliparous women who had a confirmed single viable fetus before 14 weeks of gestation. Pregnancy dating was based on first-trimester crown-rump length measurements. Research visits were conducted at 20, 28, and 36 weeks. Maternal blood samples were collected at each visit. Perinatal data were obtained from questionnaires completed by participants or from medical records.

To evaluate mid-childhood educational attainment, the POPS antenatal data were linked to the National Pupil Database (NPD) maintained by the UK Department for Education (DfE). The NPD contains individual-level assessment data reported annually by state-funded schools in England[20] (last follow-up at the end of school year 2019; Supplementary Appendix 1 and 2).

Informed consent was obtained from all POPS study participants. They were informed about the data linkage study and given the option to opt out. Data access and linkage

were performed through the Office of National Statistics Secure Research Service. All datasets were anonymised, and the study was approved by the Cambridgeshire 2 Research Ethics Committee (07/H0308/163), Cambridge Central Research Ethics Committee (18/EE/0036), and the Confidentiality Advisory Board (18/CAG/0024).

*Exposures and Covariates*

Exposures in the study included maternal hemoglobin (Hb) concentrations at 12 and 28 weeks of gestation, the change in Hb in g/L between 12-28 weeks (delta Hb), top study-specific decile of Hb concentration, and maternal anemia, defined as Hb concentration below 110g/L in the first trimester or below 105g/L in the second and third trimesters[16].

Covariates included in the analysis were infant factors, including gestational age, sex, and season of birth; maternal factors, including age and BMI at recruitment, ethnicity, partner status, smoking history; and socio-economic factors, including maternal occupation, index of multiple deprivation (IMD score; 2007), school funding type, and year of assessment. Childhood health and morbidity data were extracted from Hospital Episode Statistics (HES; provided via NHS Digital) relating to (i) emergency department attendances, (ii) hospital inpatient stays, and (iii) hospital outpatient appointments to compile a pre-specified list of conditions (Supplementary Appendix 3).

The primary study outcome was a series of binary variables indicating whether children met expected educational standards at ages 5, 6, and 7. At age 7, the outcomes consisted of four different learning domains: reading, writing, mathematics,

and science[21]. Detailed information regarding the assessment of educational attainment at the ages of 5, 6, and 7 in the UK is provided in Supplementary Appendix 2. Pregnancy complications (small-for-gestational age, pre-eclampsia, preterm birth, and gestational diabetes) were assessed as binary outcome variables (defined in Supplementary Appendix 1).

*Statistical Analyses*

Statistical analyses were conducted according to a predetermined analysis plan approved by all authors. Numerical data were presented as mean±standard deviation or N(%) for categorical data. Associations between predictor variables and educational outcomes were initially assessed using generalised additive models with maternal Hb concentrations as a continuous exposure variable or maternal anemia as a categorical exposure variable; models were run both unadjusted and fully adjusted for relevant covariates. Generalised additive modelling was used to allow non-parametric model fitting with relaxed assumptions about the functional form of the relationship between maternal Hb parameters and outcomes of interest. Models were constructed by iteratively fitting weighted additive models through backfitting, and were specified using the R package 'gam'[22]. Our models specified a nonlinear term for the effect maternal Hb on the risk of each outcome, estimated using cubic splines. The backfitting algorithm was a Gauss-Seidel method for fitting additive models by iteratively smoothing partial residuals. Where relationships between the predictor variables and the log-odds or logit transformed mean of the outcomes were found to be essentially linear using this approach, further analyses were conducted using generalised linear regression models.

Missing values for certain covariates were imputed using chained equations (MICE) under a 'missing-at-random' assumption. The imputation models included relevant variables, and 20 imputed datasets were generated using the "mice" package in R, using predictive mean matching or linear regression imputation for continuous variables and logistic regression for categorical variables. Analyses were performed on each dataset, and the results were pooled using Rubin's rules.

The study was powered to detect a 35% difference in the percentage of children failing to attain expected educational standards at age 5 in the anaemic versus non-anaemic group (28 weeks) at 80% power with alpha=0.05 (requiring a minimum of 312 mothers with anemia at 28 weeks).

All analyses were conducted using R version 3.6.123[23], and two-sided p-values were reported. The study adhered to the STROBE guidelines for reporting (Supplementary Table 5).

## Results

Data from 78% (3285/4212) of birth cohort participants was available, representing 89% (3285/3677) of those eligible for inclusion (Figure 1). The characteristics of the analytic sample were similar to those of the birth cohort as a whole (Supplementary Table 1). 2.3% (73/3162) of participants were anaemic at 12 weeks of pregnancy, rising to 12.2% (314/2571) by 28 weeks (Table 1). The median delta Hb (drop in Hb between 12 and 28 weeks) was 13g/L (IQR 8-18g/L; Table 1).

235

236 *Pregnancy outcomes*

237 There was no association between maternal Hb concentration at 12 weeks and the
238 likelihood of any tested pregnancy complication (Supplementary Table 2).

239 Higher maternal Hb at 28 weeks was associated with decreased birthweight
240 (Supplementary Fig 2a) and increased risk of being small-for-gestational age (aOR
241 1.26, 95%CI 1.11-1.59 per 1g/L increase in Hb; p=0.002; Table 2). Higher maternal
242 Hb at 28 weeks was also associated with an increased risk of preterm birth (aOR 1.38,
243 95%CI 1.11-1.81; p=0.005; Table 2 & Supplementary Fig 2c). In view of the
244 association between maternal anemia and pre-term birth, subsequent analysis of the
245 relationship between maternal Hb and educational outcomes included only children
246 born at term (96%; 3140/3285). A higher delta Hb (i.e. greater drop in Hb between 12
247 and 28 weeks) was associated with increased birthweight (Supplementary Fig 2b) and
248 reduced risk of being small-for-gestational age (aOR 0.81, 95%CI 0.67-0.98 per 1g/L
249 increase in delta Hb; p=0.03; Table 2).

250

251 *Educational outcomes*

252 *(i) Maternal hemoglobin*

253 There was no association between maternal Hb concentration at 12 weeks and
254 likelihood of attaining expected educational standards at any age (Figure 2a; data
255 shown age 5).

At 28 weeks, lower maternal Hb was associated with a higher likelihood of not attaining expected educational standards aged 5 (Figure 2b). The observed association was essentially linear, with no evidence of an adverse effect of higher maternal Hb. No statistically significant non-linear associations were observed between maternal Hb at 28 weeks and any educational outcome. The associations were substantively unchanged in sensitivity analyses using a 'healthy' population only, i.e. excluding any participants who had experienced severe perinatal or childhood health complications (Supplementary Figure 3).

There was no evidence that the presence of pregnancy complications mediated any associations between maternal Hb and educational outcomes (all interaction terms non-significant; Supplementary Table 3).

*(ii) Maternal anemia*

At 12 weeks, there was no association between maternal anemia and educational outcome (Table 3). Children of mothers who were anaemic at 28 weeks had ~40% increased risk of not attaining expected educational standards aged 5 (aOR 1.42, 95%CI 1.03-1.95; p=0.03; Table 3). However there was no association between maternal anemia and educational performance at older ages (6-7 years; Table 3).

*(iii) Other parameters*

There was no evidence for an association between higher maternal Hb at 28 weeks (top cohort-specific decile) and poorer educational attainment (Supplementary Table 4). The magnitude of the drop in maternal Hb between 12-28 weeks of gestation (delta Hb) was not associated with poorer educational performance at any age (Supplementary Table 4).

## Comment

*Principal findings*

In this high-resource obstetric setting lower maternal Hb at 28 weeks was associated with poorer educational attainment aged 5 among children born at term. Children whose mothers were anaemic at this late stage of pregnancy had ~40% increased risk of not attaining educational targets. There was no evidence of a U-shaped association between maternal Hb and childhood educational attainment.

*Result in the context of what is known*

The mechanism of the association between maternal anemia in late pregnancy and poorer educational outcomes aged 5 is unclear; in particular our data indicate that it is not mediated by adverse birth outcomes or reduced fetal growth. Previous studies examining the relationship between maternal iron status and neurodevelopment aged 4-5 years have shown mixed results, with either no association[24], or possible positive benefit from higher maternal iron status on memory[25] and attention[26]. A small South African study specifically assessing brain morphology found that maternal anemia, but not childhood anemia, was associated with smaller brain volumes and altered structural brain development at 2-3 years[27].

However we also found that the relationship between maternal anemia and poor educational outcomes does not persist later into childhood (age 6-7). A possible explanation is that the assessments performed at ages 6-7 were focused on core aspects of educational attainment (Supplementary Appendix 2), rather than the more

holistic approach to development taken at age 5. This is in keeping with previous data from the ALSPAC cohort, where no association was found between maternal Hb during late pregnancy and child IQ aged 8[28].

*Clinical implications*

These findings suggest that maternal Hb status may have less relevance to childhood outcomes at later ages, as maternal and child diet and health factors diverge more. It is reassuring for families and clinicians that even if there is an adverse impact of maternal anemia on early childhood neurodevelopmental outcomes, these are not likely to persist in the longer term.

Higher maternal Hb in late pregnancy or lower delta Hb may indicate a lack of physiological plasma volume expansion as pregnancy progresses. Failure to adequately expand the maternal plasma volume is a feature of pregnancies affected by placental insufficiency or underlying maternal cardiovascular disease[9]. In keeping with previous studies[29], we found that high Hb at 28 weeks and low delta Hb were both associated with adverse pregnancy outcomes, in particular SGA and preterm birth. However there was no association between these parameters and childhood educational attainment. We have previously shown that placental insufficiency is associated with reduced educational attainment, but only in the context where it is severe enough to be associated with an estimated fetal weight <10$^{th}$ centile[10].

There was no evidence to support a U-shaped associated between maternal Hb and educational outcomes in mid-childhood in this large prospective cohort. This is an important finding from the perspective of a proactive approach to hemoglobin-based

screening for maternal anemia and iron supplementation as currently recommended by the British Association of Haematology guidelines and others[16]. This is particularly important in view of the increasing use of intravenous iron during pregnancy, where there is no gastrointestinal regulation of iron uptake and hence reduced protection against maternal iron overload[30]. However our findings are reassuring about the long-term impacts of high hemoglobin for childhood educational attainment.

*Strengths and limitations*

Strengths of the study include the use of a large prospective birth cohort with meticulous phenotyping and high follow-up rates, reducing the potential for attrition bias in the cohort. A major strength is the use of standardised and validated educational testing, using methodology bench-marked against all children at UK state schools. The pragmatic approach of using educational attainment as a primary outcome has the advantage of real-world relevance to the developing child, although it risks missing subtle deficits in specific domains, for example attention.

The main limitation of study is that we did not directly measure maternal ferritin levels or adherence to iron supplementation recommendations. The study context is a typical high-resource European obstetric setting where the majority of women have access to adequate nutrition during pregnancy. Our population had low incidence of maternal anemia at 12 weeks (2.3%) and accessed well-resourced standardised obstetric care. While results of this study can shed light on underlying associations between mild anemia and educational attainment and are relevant for discussions of population-level supplementation recommendations in high-resource settings, they are not generalisable to settings where there is a high prevalence of severe anemia and poor

obstetric outcomes. We also did not have access to a direct measure of childhood Hb. However previous systematic review data only suggests modest correlation between maternal and infant iron status[15].

*Conclusions*

Maternal anemia in late pregnancy is associated with a reduced likelihood of attaining expected educational standards aged 5, however we found no evidence that maternal Hb affects childhood educational attainment by age 6-7 years.

**Author contributions**

CEA and LO had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. GCS, HW, and CEA designed the study. CEA, HW, LO and US acquired and/or analyzed data. CEA and LO drafted the manuscript, which was revised by all authors. All authors have approved the published version and agreed to be accountable for all aspects of the work.

This work was produced using statistical data from ONS. The use of the ONS statistical data in this work does not imply the endorsement of the ONS in relation to the interpretation or analysis of the statistical data. This work uses research datasets which may not exactly reproduce National Statistics aggregates.

**Data availability**

The raw data from the POPS study are not publicly available, due to the nature of the consent given by participants in the original study. Requests for POPS supplemental information, including raw data, can be made to Mrs Sheree Green-Molloy at the Department of Obstetrics and Gynaecology, Cambridge University, UK (paoandghod@medschl.cam.ac.uk). The educational data used in the study are a bespoke extract from the National Pupil Database (NPD) containing anonymised individual pupil level results of routinely administered national assessments. The data controller for the NPD is the UK Department for Education, Department of Work and Pensions, Higher Education Statistics Authority, HM Revenue & Customs. The NPD was accessed for this study via the Office of National Statistics Secure Research Service (ONS SRS) under a data-sharing agreement with the University of Cambridge.

Access to NPD is available to researchers on application: https://www.gov.uk/guidance/apply-for-department-for-education-dfe-personal-data.

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493 **Table 1 Maternal hemoglobin parameters**

| Parameter | | Sampling at 12 weeks N=3162 | Sampling at 28 weeks N=2571 |
|---|---|---|---|
| Maternal Hb | | 127 (122 – 132) | 114 (109 – 119) |
| Maternal anemia (Hb <110g/L) | | 73 (2.3) | 741 (28.8) |
| Maternal anemia (Hb <105g/L) | | 26 (0.8) | 314 (12.2) |
| Delta Hb (absolute change) | | NA | 13 (8 - 18) |
| Delta Hb (percentage change) | | NA | 10.1 (6.2 - 13.6) |
| High delta Hb | >5g/L change | NA | 2056 (84.0) |
| | >11% change | NA | 1052 (43.0) |
| | >14g/L change | NA | 1088 (44.4) |

494
495 Numerical values expressed as median (IQR), categorical variables as n (%). All
496 hemoglobin (Hb) values expressed as g/L. Delta Hb defined as the difference
497 between Hb measured at 12 and 28 weeks. n=2448 observations where delta Hb
498 could be calculated, i.e. Hb concentrations available at both 12 and 28 weeks of
499 gestation. N=sample size. NA=not appropriate.
500
501

**Table 2 Association between maternal hemoglobin at 28 weeks and pregnancy complications**

| | | Hb at 28 wks | | | Anemia at 28 wks | | | Delta Hb | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | aOR | 95% CI | p | aOR | 95% CI | p | aOR | 95% CI | p |
| GDM | N=154 | 0.95 | 0.67-1.06 | 0.16 | 1.18 | 0.63-2.05 | 0.57 | 1.11 | 0.88-1.50 | 0.28 |
| Pre-eclampsia | N=233 | 1.11 | 0.85-1.26 | 0.67 | 1.10 | 0.65-1.77 | 0.70 | 1.04 | 0.83-1.30 | 0.72 |
| SGA | N=296 | 1.26 | 1.11-1.59 | 0.002 | 0.52 | 0.29-0.85 | 0.02 | 0.81 | 0.67-0.98 | 0.03 |
| Pre-term birth | N=142 | 1.38 | 1.11-1.81 | 0.005 | 0.69 | 0.33-1.30 | 0.29 | 0.86 | 0.65-1.13 | 0.27 |

Hb: maternal hemoglobin measured in g/L (n=2571), Anemia at 28 weeks defined as maternal HB <105g/L, with mothers who were not anaemic as the referent group (2257/2571). Delta Hb defined as the difference between Hb measured at 12 and 28 weeks (n=2448).

GDM: gestational diabetes mellitus; SGA: small-for-gestational age, defined as <10$^{th}$ centile for gestational age and sex on British 1990 growth charts; aOR: adjusted odds ratio; N: sample size.

Covariates included in all models: maternal factors (age at pregnancy, BMI at recruitment, ethnicity, partner status, smoking history), infant factors (gestational age, sex), socio-economic factors (IMD score, maternal occupation).

**Table 3 Association between maternal anemia and not achieving expected educational standard at each age/domain**

| Education parameter | | Maternal anemia | | | |
|---|---|---|---|---|---|
| | | 12 weeks | | 28 weeks | |
| | | OR (95%CI) | p | OR (95%CI) | p |
| Age 5 | *Unadjusted* | 1.57 (0.91-2.63) | 0.09 | 1.45 (1.09-1.91) | 0.01 |
| | *Adjusted* | 1.4 (0.76-2.51) | 0.27 | 1.42 (1.03-1.95) | 0.03 |
| Age 6 | *Unadjusted* | 1.11 (0.51-2.15) | 0.77 | 1.06 (0.72-1.51) | 0.77 |
| | *Adjusted* | 0.94 (0.41-1.92) | 0.87 | 0.98 (0.65-1.44) | 0.91 |
| Age 7-Reading | *Unadjusted* | 0.97 (0.46-1.85) | 0.93 | 1.05 (0.74-1.46) | 0.79 |
| | *Adjusted* | 0.87 (0.39-1.74) | 0.71 | 0.91 (0.62-1.3) | 0.61 |
| Age 7-Writing | *Unadjusted* | 1.02 (0.54-1.82) | 0.95 | 0.87 (0.63-1.19) | 0.40 |
| | *Adjusted* | 0.86 (0.43-1.61) | 0.64 | 0.76 (0.54-1.07) | 0.13 |
| Age 7-Maths | *Unadjusted* | 0.94 (0.45-1.79) | 0.86 | 1.25 (0.9-1.72) | 0.18 |
| | *Adjusted* | 0.82 (0.37-1.62) | 0.58 | 1.1 (0.77-1.55) | 0.60 |
| Age 7-Science | *Unadjusted* | 1.54 (0.7-3.02) | 0.24 | 1.23 (0.81-1. 28) | 0.32 |
| | *Adjusted* | 1.4 (0.61-2.88) | 0.39 | 1.05 (0.67-1.59) | 0.39 |

Odds ratios (OR) with 95% confidence intervals are displayed with participants born to mothers without anemia at corresponding time point as the referent group (N=73/3089 for 12 weeks, N=314/2257 for 28 weeks). Anemia at 12 weeks defined as <110g/L, anemia at 28 weeks defined as <105g/L. N=sample size.

For adjusted models, covariates included in all models: maternal factors (age at pregnancy, BMI at recruitment, ethnicity, partner status, smoking history), infant factors (gestational age, sex, birth seasonality, childhood physical health), socio-economic factors (IMD, school funding type, academic year, maternal occupation), potential effect modifiers (infant small-for-gestational age status, maternal pre-eclampsia, maternal gestational diabetes mellitus).

## Figure titles and legends

**Figure 1 Number of participants from recruitment to POP study through identification of analytic sample.**

89% of participants who were eligible for linkage (3285/3677) are included in the analytic sample, which represents 78% of the total participants originally recruited (3285/4212).

**Figure 2 a) Relationship between not meeting educational standards aged 5 and maternal hemoglobin (Hb; g/L) at 12 weeks (n=3005) b) Relationship between not meeting educational standards aged 5 and maternal hemoglobin (Hb; g/L) at 28 weeks (n=2436)**

Regression lines (solid black lines) derived from generalised additive models adjusted for maternal factors (age at pregnancy, BMI at recruitment, ethnicity, partner status, smoking history), infant factors (gestational age, sex, birth seasonality, childhood physical health), socio-economic factors (IMD, school funding type, academic year, maternal occupation), potential effect modifiers (infant small-for-gestational age status, maternal pre-eclampsia, maternal gestational diabetes mellitus). 95% confidence intervals shown as dashed lines and cohort average as solid red line.