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Maternal Hb during pregnancy and offspring's educational achievement: a prospective cohort study over 30 years

Mohammad Fararouei[1], Claire Robertson[2], John Whittaker[3], Ulla Sovio[4], Aimo Ruokonen[5], Anneli Pouta[6], Anna-Liisa Hartikainen[7], Marjo-Riitta Jarvelin[4,6,8]†* and Elina Hyppönen[9]†*

[1]*Faculty of Health, Yasuj University of Medical Sciences, Yasuj, Iran*
[2]*School of Life Sciences, University of Westminster, London, UK*
[3]*London School of Hygiene and Tropical Medicine, London, UK*
[4]*Department of Epidemiology and Public Health, Imperial College London, Norfolk Place, St Mary's Campus, London W2 1PG, UK*
[5]*Institute of Diagnostics, University of Oulu, Oulu, Finland*
[6]*National Institute of Health and Welfare, Oulu, Finland*
[7]*Department of Clinical Medicine/Obstetrics and Gynaecology, University of Oulu, Oulu, Finland*
[8]*Institute of Health Sciences, University of Oulu, Biocenter Oulu, PO Box 5000, Fin-90014 Oulu, Finland*
[9]*MRC Centre of Epidemiology for Child Health, Centre for Paediatric Epidemiology and Biostatistics, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK*

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The aim of the present study was to examine the association between maternal Hb levels during pregnancy and educational achievement of the offspring in later life. We analysed data obtained from the Northern Finnish Birth Cohort Study conducted in 1966, in which, data on mothers and offspring from pregnancy through to the age of 31 years were collected. The cohort comprised 11 656 individuals born from singleton births (51 % males and 49 % females). Maternal Hb levels were available from the third, seventh and ninth gestational months. Educational achievement was measured as school scores (range 4–10) taken at the ages of 14 (self-reported questionnaires) and 16 (school reports) years as well as the highest level of education at the age of 31 years. The present results showed a direct positive association between Hb levels and educational achievement in later life. After adjustment for sex, birth weight, birth month and a wide range of maternal factors (parity, smoking, mental status, whether pregnancy was wanted or not, education, social class and marital status), only maternal Hb levels that were measured at the ninth month were significantly associated with the offspring's school performance. If the levels were ≥ 110 g/l at all the three measurement points, offspring not only had better school scores at the ages of 14 and 16 years ($\beta = 0{\cdot}048$, $P = 0{\cdot}04$ and $\beta = 0{\cdot}68$, $P = 0{\cdot}007$, respectively), but also had an increased odds of having a higher level of education at the age of 31 years (OR = 1·14, $P = 0{\cdot}04$). The present study suggests that low maternal Hb levels at the final stages of pregnancy are linked to the poorer educational achievement of the offspring. If our observation is confirmed, it would suggest that Fe prophylaxis even at fairly late stages of pregnancy may be beneficial for the subsequent health of the offspring. However, more studies are needed to fully establish the potential pathways and the clinical importance of the present findings.

School achievement: Higher education: Maternal Hb: Cohort study

Hb is an Fe-containing metal protein found in the erythrocytes, and is responsible for O_2 transportation in vertebrates. In addition to being bound to Hb, Fe is found in cells throughout the human body, and is crucial for multiple metabolic processes, which range from DNA synthesis to electron transportation[1,2]. As defined by the WHO, Fe deficiency is the most common nutritional disorder and the leading cause of anaemia in the world. A quarter of the world's population, i.e. 1·6 billion people, are estimated to be anaemic, with pregnant women and children being the most vulnerable to this deficiency[3]. Anaemia is commonly defined as Hb levels below 138 g/l in men, 121 g/l in women, and 110 g/l in pregnant women and in children.

Through its complex role in oxidative metabolism and in the synthesis of neurotransmitters and myelin, the importance of Fe in normal neurological functions is increasingly being recognised[4]. However, with 41·5 % of the global population of pregnant women (European 18·7 % and African 55·8 %)

Abbreviation: NFBC, Northern Finnish Birth Cohort.

* **Corresponding authors:** M.-R. Jarvelin and E. Hyppönen, email m.jarvelin@imperial.ac.uk; e.hypponen@ich.ucl.ac.uk

† Both authors M.-R. J. and E. H. contributed equally to the work.

being anaemic[5], there is still a shortage of studies examining the association between Fe deficiency and early brain development.

Studies in rodents have shown that pregnant rats fed on an Fe-deficient diet during both early gestation and lactation give birth to offspring with lower Fe concentrations in the brain[6,7]. Fe supplementation in mid-gestation or immediately following delivery did not raise the brain Fe concentration as expected, with dams and pups exhibiting significantly poorer cognitive performance. Human studies also suggest an association of Fe deficiency and supplementation, particularly in early life, with long-term cognitive development[8–10]. However, there are no studies examining the relationship of maternal Fe status (as a marker for pre-natal exposure) with offspring's long-term cognitive development. Using data obtained from the 1966 Northern Finnish Birth Cohort (NFBC 1966) study, we examined the association between maternal Hb levels during pregnancy and later educational achievement to obtain further insights into the possible long-term influences of Fe status *in utero*.

Methods

Population

The NFBC 1966 dataset comprises data pertaining to the births in the two northernmost provinces of Finland (i.e. Oulu and Lapland) during 1966 (live births *n* 12 058, coverage 96 %)[11]. Data on mothers were collected through questionnaires/interviews and records at communal maternal welfare centres during routine antenatal visits; mothers were recruited for the study between the twenty-fourth and the twenty-eighth gestational weeks. Of these, 9·7 % of the data were completed in later pregnancy or after birth. Children were followed into adulthood, and data were collected at birth and at 14 and 31 years of age using hospital records/official national registers and self-administered questionnaires/interviews. In the present study, we analysed data on individuals with written informed consent and born from singleton pregnancies. Data pertaining to socio-demographic status, behaviour, whether pregnancy was wanted or not, mother's educational status, mother's emotional status and smoking were extracted from this dataset for analysis[12,13].

Measures

Maternal Hb levels were measured at the third, seventh and ninth gestational months during antenatal visits at health centres or hospitals. Seven different methods available at that time were used, i.e. Tallqvists table, Ljungberg, Sicca, Sahli, Vatatron-Fotom, Erka and Linson Junior. In order to make the results comparable, they were standardised and scaled to grams per litre by clinical and laboratory experts and by the research team. Information on maternal Fe supplementation was not available.

Data on school performance were acquired at 14 and 16 years of age through scores given by teachers. Scores ranged from 4 to 10 on theory subjects such as physics, mathematics, chemistry, the first and second national languages, foreign languages, biology, religion/ethics, social studies, history, geography and natural sciences (given as separate scores/subject and as an overall performance score), and overall score of all subjects, which was calculated as the average of scores given on theory subjects and practical subjects (i.e. music, visual art, health education, crafts, physical education and household economics, available at both 14 and 16 years of age). Information on school performance at the age of 14 years was obtained through self-administered questionnaires sent to the adolescents or to the parents, if the adolescents did not respond (total response *n* 9983, 86 % of the study sample). Information on school achievement at the age of 16 years was extracted directly from school reports (*n* 10 474, 90 % of the study sample). School scores at the ages of 14 (self-reported) and 16 (reported by the school) years were highly correlated (intraclass correlation coefficient = 0·9), suggesting a good reliability for the self-reported scores. Information on higher educational status, with details of university degree if present, was acquired through a postal questionnaire at the age of 31 years (*n* 8427, 72 % of the study sample). The present study was conducted in agreement with the Declaration of Helsinki, and all procedures involving human subjects were approved by the University of Oulu ethics committee. Written informed consent was obtained from all the subjects.

Statistical analysis

The ANOVA or Student's *t* test was used to run the statistical analysis to examine the association between background variables and maternal Hb levels during pregnancy and school scores of the offspring (Table 1). The χ^2 test was used to analyse the association between background covariates and the level of education at the age of 31 years. The association of persistent anaemia (Hb < 110 g/l measured at all points, *n* 39) and intermittent anaemia (*n* 1440, Hb < 110 g/l in either the third (*n* 823), seventh (*n* 869) or ninth (*n* 376) month of gestation) with educational achievements was also examined by fitting separate models. Multiple linear regressions were run for continuous outcomes (school scores) by assuming a linear relationship between the variable and its predictors. Residual plots were checked for the model assumptions. Logistic and polytomous regressions were run for binomial and categorical variables. Analyses were first performed using linear or logistic regression to examine the sex-adjusted association between the predictors and the outcomes. Among the available information (i.e. sex, gestational age, birth weight and length, child's calendar month of birth, mother's educational status, whether pregnancy was wanted or not, social class, parity, mother's marital status at pregnancy, mother's smoking status during pregnancy, mother's mental status, father's social status, mother's weight, mother's height and child's Fe supplementation during infancy), factors were selected as covariates in the final model if a significant improvement in the goodness of fit of the model was achieved. The proportion of participants with missing data varied by covariate, ranging from 0 % for sex to 27·7 % for information on higher education at the age of 31 years. We imputed (five times) the data to replace the missing values using the multivariate imputation by chained equations package[14]. Statistical analysis was run by R (2.3.0) package[15].

Table 1. Maternal Hb at the ninth month of pregnancy, offspring school score at the age of 16 years and proportion with higher education at the age of 31 years by background variables in the 1966 Northern Finnish Birth Cohort study

(Mean values, standard deviations, *n* and percentages)

	Maternal Hb at the ninth month of pregnancy			Offspring school score at the age of 16 years			Offspring with higher education	
	Mean	SD	*n*	Mean	SD	*n*	*n*	%
Sex								
Female	124·29	10·61	5433	7·83	0·89	5150	2286	52·00
Male	124·64	10·82	5659	7·21	0·91	5324	1229	30·49
Unknown	NA	NA	0	NA	NA	0	NA	NA
P	0·086			<0·001			<0·001	
Birth weight (kg)								
>2·5	125·33	12·88	256	7·37	0·92	273	77	35·48
≤2·5	124·45	10·67	10 835	7·52	0·95	10 200	3438	41·88
Unknown	136·00	NA	1	8·3	NA	1	NA	NA
P	0·28			0·01			0·07	
Child's order*								
First	124·79	10·47	546	7·67	0·93	531	229	54·14
Second	125·36	10·31	2801	7·68	0·94	2717	1151	52·77
Higher	124·25	10·86	7190	7·47	0·95	6957	2090	37·08
Unknown	122·41	10·75	555	6·86	0·92	269	45	24·06
P	<0·001			<0·001			<0·001	
Mother's age (years)								
>20	124·14	10·35	831	7·35	0·90	704	201	35·45
20–35	124·61	10·65	8551	7·54	0·96	8114	2812	43·16
<35	123·91	11·22	1664	7·49	0·94	1609	490	37·61
Unknown	124·54	11·72	46	7·19	0·95	47	12	28·57
P	0·034			<0·001			<0·001	
Mother's civil status*								
Married	124·55	10·72	10 670	7·53	0·95	10 077	3419	42·17
Single	122·13	10·59	406	7·25	0·92	382	90	29·51
Unknown	126·00	8·45	16	7·55	1·23	15	6	42·86
P	0·001			<0·001			0·001	
Mother's educational status*								
None	124·01	10·77	139	7·13	0·90	132	20	19·61
Basic	124·22	10·86	7105	7·36	0·92	6609	1778	33·31
Higher	125·07	10·39	3682	7·84	0·94	3560	1672	58·54
Unknown	121·97	11·48	166	7·35	0·94	173	45	34·09
P	<0·001			<0·001			<0·001	
Family social class*								
No job	124·22	10·61	3772	7·37	0·94	3450	976	35·13
Farmer	124·56	11·58	2451	7·41	0·91	2367	573	29·19
Unskilled	123·63	10·51	948	7·39	0·92	864	255	36·90
Skilled	124·93	10·28	3759	7·76	0·96	3641	1663	58·03
Unknown	123·03	10·52	162	7·44	0·92	152	48	37·21
P	0·0013			<0·001			<0·001	
Mother is a smoker								
No	124·77	10·77	9219	7·55	0·95	8753	3028	42·88
Yes, cigar	123·08	10·34	1374	7·33	0·96	1250	361	36·46
Yes, other	122·72	10·03	270	7·34	0·92	243	70	36·65
Unknown	122·80	11·02	229	7·43	0·93	228	56	30·27
P	<0·001			<0·001			<0·001	
Mother was depressed during pregnancy*								
No	124·80	10·66	9392	7·55	0·95	8858	3065	42·86
Yes, mild	122·92	10·92	1264	7·31	0·94	1187	342	37·09
Yes, severe	122·02	10·41	229	7·17	0·98	209	43	25·00
Unknown	121·63	11·22	207	7·51	0·92	220	65	35·91
P	<0·001			<0·001			<0·001	
Was the pregnancy wanted?*								
Yes	125·21	10·53	6915	7·61	0·95	6580	2458	46·47
Yes, but later	123·63	10·64	2714	7·43	0·940	2483	734	36·77
No	122·61	11·44	1247	7·23	0·914	1181	263	27·45
Unknown	121·87	11·00	216	7·42	0·93	230	60	32·79
P	<0·001			<0·001			<0·001	

NA, not available.

* Based on the information provided by mothers (self-reported). Unknown group was not included in the statistical tests.

Results

Table 1 shows the associations between confounding factors, exposure and educational outcomes. Children from higher social class, married families and wanted pregnancies, and female offspring and first or second born had significantly better school performance at the age of 16 years ($P<0·001$ for each comparison), and were more likely to have completed a university degree by the age of 31 years ($P<0·001$).

Data on Hb levels were available for 9470 expectant mothers; of these, 84·79 % (*n* 8030) did not have any form of anaemia at any stage during pregnancy. Thirty-nine expectant mothers (0·41 %) had persistent anaemia, and 1440 (15·21 %) had intermittent anaemia at third, seventh and/or ninth month of gestation (but were not anaemic at all points).

Adjusted for sex, maternal Hb at all stages of pregnancy was associated with school scores at the ages of 14 and 16 years ($P<0·01$ for all comparisons), while associations with higher education were observed for concentrations at the seventh and ninth months only. After full adjustment for potential confounders (sex, birth weight, calendar month of birth, mother's educational status, whether pregnancy was wanted or not, social class, parity, mother's marital status at pregnancy, mother's smoking status during pregnancy and mother's mental status), the associations between higher maternal Hb levels and school performance persisted for measures taken at 9 months, but not for measures taken at earlier stages of pregnancy (Table 2). Some suggestion for an association with school performance at the age of 16 years was also observed for maternal concentrations at 3 months in the imputed case analyses ($P=0·04$), but not in the complete case analyses. After full adjustment, maternal Hb at any single time point was not associated with the higher final education. However, offspring of mothers with anaemia at least in some stage of pregnancy (Hb < 110 g/l at one or more points) appeared to have lower school scores, and they were also less likely to have completed a higher education degree at the age of 31 years (Table 2). The associations between maternal Hb and school achievement were similar in the subgroup of mothers who were non-anaemic throughout pregnancy compared with those observed in the full cohort (data not shown). There was no evidence for an interaction between Hb levels at different points of measurement and sex in relation to school scores or higher educational achievement ($P>0·15$ for all comparisons).

Discussion

Using data obtained from a large prospective cohort study, we found evidence for a direct association between maternal Hb levels during pregnancy and the educational achievement of the offspring. These data suggest long-term influences of pre-natal Fe metabolism, supporting earlier observations from animal experiments[16–20]. Previous studies in human subjects are sparse, although earlier data have suggested reduced cognitive performance after Fe deficiency during infancy/early childhood[21–26].

It is unclear what individual pathways are involved in Fe deficiencies thought to affect brain development. Plausible routes described in previous human/animal studies include the following: alteration in neurotransmitter and/or brain

Table 2. Association of maternal Hb (per 10 g/l increase) with offspring's educational achievement in the 1966 Northern Finnish Birth Cohort study

(β Coefficients or odds ratios and 95 % confidence intervals)

	Total score at the age of 14 years				Theory score at the age of 14 years				Total score at the age of 16 years				Higher final education			
	β	95 % CI	*n*	*P*	β	95 % CI	*n*	*P*	β	95 % CI	*n*	*P*	OR	95 % CI	*n*	*P*
HB3																
Sex adjusted	0·023	0·007, 0·039	8049	0·005	0·025	0·006, 0·044	7736	0·009	0·024	0·007, 0·042	8228	0·006	1·03	0·98, 1·08	6637	0·22
Fully adjusted*	0·012	−0·003, 0·027	8049	0·13	0·014	−0·003, 0·032	7736	0·11	0·012	−0·005, 0·028	8228	0·17	1·00	0·95, 1·05	6637	0·93
Fully adjusted†	0·011	−0·002, 0·024	11 656	0·11	0·012	−0·003, 0·028	11 656	0·12	0·013	−0·002, 0·029	11 656	0·08	1·01	0·97, 1·06	11 656	0·96
HB7																
Sex adjusted	0·029	0·013, 0·045	9128	0·0003	0·038	0·020, 0·057	8778	<0·0001	0·033	0·015, 0·050	9336	0·002	1·05	1·01, 1·10	7530	0·03
Fully adjusted*	0·0097	−0·005, 0·025	9128	0·20	0·017	−0·001, 0·035	8778	0·06	0·011	−0·005, 0·028	9336	0·18	1·01	0·96, 1·06	7530	0·65
Fully adjusted†	0·0096	−0·005, 0·024	11 656	0·45	0·017	−0·000, 0·033	11 656	0·051	0·012	−0·0035, 0·027	11 656	0·13	1·02	0·97, 1·06	11 656	0·45
HB9																
Sex adjusted	0·047	0·032, 0·063	9036	<0·0001	0·055	0·036, 0·073	8686	<0·0001	0·049	0·032, 0·066	9247	<0·0001	1·06	1·02, 1·11	7462	0·005
Fully adjusted*	0·028	0·013, 0·042	9036	0·0003	0·033	0·016, 0·051	8686	0·0002	0·026	0·010, 0·043	9247	0·002	1·02	0·97, 1·07	7462	0·42
Fully adjusted†	0·025	0·010, 0·037	11 656	0·0002	0·033	0·017, 0·048	11 656	<0·0001	0·026	0·012, 0·041	11 656	0·0005	1·03	0·99, 1·07	11 656	0·14
Anaemia‡																
Sex adjusted	−0·120	−0·160, −0·070	9295	<0·0001	−0·13	−0·19, −0·075	8937	<0·0001	−0·14	−0·19, −0·088	9509	<0·0001	0·71	0·62, 0·81	7666	<0·0001
Fully adjusted*	−0·048	−0·092, −0·003	9295	0·04	−0·048	−0·10, 0·005	8937	0·08	−0·061	−0·11, −0·012	9509	0·01	0·86	0·74, 0·99	7666	0·045
Fully adjusted†	−0·043	−0·085, −0·0003	11 656	0·049	−0·047	−0·095, 0·001	11 656	0·06	−0·064	−0·11, −0·016	11 656	0·01	0·86	0·76, 0·98	11 656	0·02

* Adjusted for sex, birth weight, mother's educational status, whether pregnancy was wanted or not, mother's social class, number of children, mother's marital status at pregnancy, mother's smoking status during pregnancy, mother's mental status and child's calendar month of birth.

† Models with multiple imputation on missing information, adjusted as described above.

‡ Comparison for anaemia (<110 g/l) at one or more occasions *v.* no anaemia at any stage.

energy metabolism and/or decreased myelination[9,19,27]. In the present study, maternal Hb at the final trimester (but not at the earlier stages of pregnancy) was associated with the offspring's school performance, which indicates that there could be a sensitive period for the final stages of development[28]. This would be biologically plausible as during the final trimester of pregnancy and early infancy, myelination can be altered as a result of Fe deficiency[29,30]. It is also possible that the association could have been mediated by maternal influences on Hb concentrations in early infancy, which would provide an alternative explanation for the lack of effect for the first two trimesters. Lack of association for the earlier stages of pregnancy can also be explained by the initiation of Fe supplementation to mothers diagnosed as anaemic.

Unfortunately, information on infant concentrations or on maternal Fe supplementation during pregnancy was not available from the present study. Nevertheless, based on standard clinical procedures[31], it is reasonable to assume that Fe supplementation would have been initiated for all women diagnosed as anaemic.

Longitudinal studies in human subjects examining motor development and cognitive function through to adulthood have indicated their negative relation with Fe deficiency anaemia in infancy[32–34]. Randomised control trials examining Fe status and school scores also reported a relationship between the two, with improvement in scores after Fe treatment[35,36]. Though these studies had included Fe status in addition to Hb levels in their analysis, they had failed to examine the effects of maternal Fe status during pregnancy on offspring. In addition to underlining the importance of maternal Hb level in the cognitive performance of the offspring, the present study suggested that the effect of Fe deficiency during pregnancy is long lasting. This is important, because despite previous suggestions for programming of cognitive function by maternal Fe status from animal experiments[16–20], there are very little data obtained from studies in human subjects. The effect sizes appear to be fairly modest in the present study, although the suggested 14 % lower proportion of offspring achieving higher education for anaemic mothers (compared with others) may be important. Furthermore, due to the active monitoring (and treatment) of pregnant women in Finland at the time of the study, there were very few mothers with severe anaemia, and many of the women classified here as anaemic would have received treatment. Hence, extrapolation of effect sizes to other populations should be done with caution, and it is possible that associations between maternal anaemia and offspring's school performance might be stronger for the more extreme cases of deficiency.

Some methodological issues also need to be considered in the context of these findings. It should be noted that although in most cases anaemia can reasonably be assumed to be due to Fe deficiency, we did not have Fe status measures to confirm this. Some of the reduction in maternal Hb during the mid-pregnancy is likely to be due to haemodilution (expansion of blood volume), which typically leads to an approximately 10 g/l reduction in circulating maternal concentrations. However, this would provide further support for our suggestive observation for a key role of late pregnancy, as the lowest Hb concentrations are typically observed about 28–32 weeks, after which, concentrations naturally raise again towards the end of the pregnancy in most mothers[37]. Missing data are a problem for all these types of longitudinal studies with follow-up lasting over several decades, although, on average, the participation rates in the NFBC 1966 study were fairly good (with 75 % of the target population participating at the age of 31 years). Multiple imputation was used for missing data in the main analyses, and similar results that were obtained were compared to complete case analyses in most analyses. Exception was the borderline association between maternal Hb at 3 months and school performance, which was observed for the imputed models, but not in the complete case series. This suggests that reduced power due to missing information could have contributed to non-significant findings. Multiple imputation is based on the assumption that the data are missing at random, and although there is no reason to believe that this assumption is violated in the NFBC 1966 study, possible bias due to missing information cannot be ruled out. Information on the school scores at the age of 14 years was self-reported, and is therefore subject to reporting bias. However, school-reported and self-reported scores were strongly correlated in the present study, suggesting that self-reported scores were reliable. Furthermore, level of education was the only outcome measured at the age of 31 years, and it can be argued that more detailed measures are required for reliable estimation of potential influences on adult cognitive performance.

Conclusion

The data suggest that there may be long-term influences of maternal Hb during the final stages of pregnancy on the cognitive development of offspring, a finding in urgent need of replication. If true, this observation is important for the clinical care of pregnant women, as it suggests that Fe prophylaxis even at fairly late stages of pregnancy may be beneficial for the subsequent development of the offspring. The association between maternal Hb level during pregnancy and offspring's school performance is potentially of great public health importance as Fe deficiency is highly prevalent in pregnant women (40 % worldwide). Further investigations with a wider range of mental performance indicators are needed to evaluate the relationships and mechanisms of maternal Fe and offspring's mental performance.

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