Maternal hemoglobin associates with preterm delivery and small for gestational age in two Finnish birth cohorts

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Abstract

Objective: To test whether maternal hemoglobin during pregnancy associates with offspring perinatal outcomes in a developed country. Changes in maternal hemoglobin concentration during pregnancy are partly physiological phenomena reflecting alterations of maternal blood volume. Especially hemoglobin measures outside the physiological range may influence maternal health and fetal growth with long-lasting consequences.

Study Design: We studied an unselected sample drawn from two regional birth cohorts born 20 years apart: The Northern Finland Birth Cohorts 1966 and 1986. These are two mother-and-child population-based birth cohorts together comprising 21,710 mothers and their children. After exclusions, the sample size of the current study was 20,554. Concentrations of maternal haemoglobin at first and last antenatal visits were categorized as low (lowest 10%), medium (reference) or high (highest 10%). Multinomial logistic regression analyses for categories of maternal hemoglobin and perinatal outcomes such as preterm delivery and full-term small and large for gestational age were conducted with adjustments for maternal cofactors.

Results: Low maternal hemoglobin at early pregnancy associated with decreased risk of full-term small for gestational age (adjusted OR 0.73, 95% CI [0.58, 0.93], p=0.010). At late pregnancy, low maternal hemoglobin associated with increased risk of preterm delivery (adjusted OR 1.60, 95% CI [1.26, 2.02], p<0.0005) whereas high maternal hemoglobin associated with increased risk of full term small for gestational age (adjusted OR 1.29, 95% CI [1.07, 1.56], p=0.009). Maternal hemoglobin did not show constant association with risk of large for gestational age.

Conclusion: The results from this study support evidence that both low and high maternal hemoglobin associate with adverse perinatal outcomes. Low maternal hemoglobin associated with preterm delivery and high with full-term small for gestational age. Association was mainly present when maternal hemoglobin was measured during the third trimester. These results indicate that it is important to monitor both extremes of maternal hemoglobin throughout the pregnancy.

Introduction

Both low and high maternal hemoglobin (mHb) concentration has been consistently associated with adverse perinatal outcomes such as preterm birth and fetal growth restriction (1-7) and in our own data with later developmental indices (8). Low hemoglobin and anemia (generally defined as mHb < 110 g/l) are global problems affecting both the mother and the developing child. In 2011, the global prevalence of anemia among pregnant women was 38%, which translated to 32 million mothers (9). Regionally, the prevalence of maternal anemia vary substantially from 22% in European and North American countries to 56% in Central and West Africa (10). Several environmental and behavioral maternal factors affect mHb and the developing child.

Smoking during pregnancy has been associated with placental defects, prematurity and growth restriction (reviewed in (11)). Furthermore, smoking associates with increased mHb levels, which may contribute to increased risk of adverse perinatal outcomes (7, 12). Low maternal BMI is associated with increased risk of spontaneous preterm birth whereas some studies report obesity to have a protective effect (13). However, obese mothers are in risk for hypertensive disorders, which associate with increased risk of medically indicated preterm birth (13). Mother's low education was associated with prematurity and small for gestational age (SGA) in recent meta analysis comprising of 12 European countries, although there were differences between countries (14). Nulliparous mothers are at increased risk of preterm delivery and SGA specifically if the mother is under 18 years old and maternal age 35 or more is associated with increased risk of SGA but not prematurity (15).

In the current study, we study the association between mHb and adverse perinatal outcomes within two study populations located in Finland. These populations are highly homogenous due to standardized antenatal care and pregnancy counselling, which contributes to fewer environmental confounders than in more diverse settings. Association between mHb at different time points of pregnancy and such outcomes as prematurity and small and large for gestational age (SGA and LGA) are studied.

Material and Methods

Inclusion and exclusion criteria

The study population is the mothers and children of Northern Finland Birth Cohorts (NFBC) 1966 and 1986 which are population-based birth cohorts comprising 98% (n=21,710) of all deliveries occurred in 1966 and 1985-86 in Oulu and Lapland provinces of Finland. Multiple pregnancies, individuals without both early and late mHb measurements and individuals with mHb over 5 SD from mean

(n=1,156) were excluded from the analyses resulting in final sample size of 20,554. Concentration of mHb at early pregnancy was available from 18,953 mothers and at late pregnancy from 20,035 mothers. Informed consent was obtained from study subjects for the use of their data in the study. Approval for the studies was granted by the ethics committee of the Northern Ostrobothnia Hospital District in Oulu, Finland in accordance with the declaration of Helsinki.

Predictor variables

Mean gestational week for early mHb measurement was 13.3 (SD 4.8) and for late mHb 38.2 (SD 3.4). In NFBC1966, mHb was measured with Tallquist chart, hemometer or photometer and in NFBC1986, with standard photometer. In NFBC1966, mHb was first standardized for measurement method and then mHb measures were transformed to z values [z(mHb)=(mHb mean(mHb))/SD(mHb)] separately for each cohort and pregnancy time point. Z value of mHb below 10th percentile was defined as low and above 90th percentile as high mHb while the middle 80% was used as reference.

Perinatal outcomes

Children born before 37 weeks of gestation were defined as preterm. SGA and LGA were analysed from full-term children (gestational age 37 weeks or more) only. SGA was defined as below 10^{th} percentile and LGA as above 90th percentile of the Finnish national reference according to (16).

Covariates

Following factors were used as covariates in the statistical models: maternal smoking, maternal hypertensive disorders, maternal pre-pregnancy body mass index (BMI), maternal socioeconomic status (SES), parity and maternal age. Maternal smoking was categorized as not smoked during pregnancy (reference, n=15,581), smoked, but not after second month of pregnancy (n=986) and smoked after second month of pregnancy (n=3,701). Maternal hypertensive disorders were defined as described in (17): Normotensive (reference, n=13,535), gestational hypertension (n=1,253), pre eclampsia (n=423), chronic hypertension (n=881) and superimposed pre-eclampsia (n=208). Maternal SES was categorized as professionals (reference, n=3,697), skilled workers (n=5,981), unskilled workers (n=3,539) and housewives, farmers and farmer's wives (n=6,906). Parity was dichotomized as nulliparous (reference, n=6,813) and multiparous (n=13,712). Maternal pre pregnancy BMI (weight in kg/(height in m)2) and age were used as continuous variables. Cohort was included in the models,

NFBC1966 as a reference (n=11,554) and NFBC1986 (n=9,000). Sex of the child was not included in the models because it did not associate with prematurity in the current population and SGA and LGA were determined from sex specific growth curves (16).

Statistics

Data from two cohorts were pooled. Differences in maternal and fetal characteristics between the cohorts were analyzed with independent samples t test for continuous variables and chi squared test of independence with subsequent post hoc analyses for categorical variables. Association between mHb at different time points of pregnancy and perinatal outcomes was analyzed using multinomial logistic regression (MLR). Odds ratios (OR) and 95% confidence intervals (95% CI) were recorded and p-values according to Wald's test that were below 0.0125 (0.05/4 tests) were considered statistically significant. Association was analyzed without adjustments (base model), with adjustment for cohort, maternal smoking and maternal hypertensive disorders (model 1) and with adjustment for cohort, maternal smoking, maternal hypertensive disorders, pre-pregnancy BMI, SES, parity and maternal age at delivery (model 2). Statistical analyses were conducted using R software package version 3.5.0 (18).

Results

Characteristics of the sample population

Distribution of offspring sex, maternal age and parity were similar between the cohorts (table 1). Other maternal and fetal characteristics changed within the 20 years between the cohort initiations. Number of mothers with low mHb at any point of pregnancy was lower in NFBC1966 than in NFBC1986 whereas number of housewives was considerably higher in NFBC1966. Furthermore, number of mothers with either gestational or chronic hypertension was higher in NFBC1966.

Multinomial logistic regression for perinatal outcomes

As shown in table 2, low mHb at late pregnancy associated with increased risk of prematurity (fully adjusted OR (aOR) 1.60, 95% CI [1.26, 2.02], $p < 0.0005$). Associations between mHb and SGA and LGA are indicated in table 3. Low mHb at early pregnancy associated with decreased risk of SGA (aOR 0.73, 95% CI [0.58, 0.93], $p = 0.010$) and high mHb at late pregnancy with increased risk of SGA (aOR 1.29, 95% CI [1.07, 1.56], $p = 0.009$, table 2). Low mHb at early pregnancy associated with increased risk of

LGA; however, the association was not statistically significant after adjustment for maternal cofactors. High mHb at early pregnancy associated with decreased risk of LGA in fully adjusted model but not in other models. Results are shown separately for each cohort in Supplementary table 1. To characterize spontaneous preterm delivery and normotensive SGA, we conducted additional MLR analyses for pregnancies without maternal hypertensive disorders as these have been shown to associate with preterm delivery as well as SGA (reviewed in (19)). As shown in supplementary table 2, similar to main analyses, low mHb at late pregnancy was associated with increased risk of spontaneous preterm delivery (aOR 1.65, 95% CI [1.27, 2.15], $p < 0.0005$). High mHb at late pregnancy was associated with increased risk of normotensive full-term SGA in model 1 (OR 1.34, 95% CI [1.08, 1.66], $p = 0.009$) and borderline significant in other models.

Sensitivity analyses

As we do not have the exact gestational age at the last antenatal visit for all mothers, we were not able to estimate the effect of exact mHb measurement timing on the perinatal outcome. This is critical specifically with the case of prematurity, because during normal pregnancy, mHb decreases until 20 weeks of gestation and then begins to increase around 30 weeks of gestation (20). To confirm that our results are not due to normal mHb change during pregnancy, we conducted sensitivity analyses such as i) MLR of individuals with available information about gestational age at last antenatal visit (n=7,281), ii) MLR of pregnancies with birth at 32 weeks of gestation or more and iii) MLR of gestational age-adjusted late pregnancy mHb. These analyses showed similar results with the main analyses (Supplementary tables 3-5). Association between prematurity and low mHb at late pregnancy was not statistically significant when gestational age at last antenatal visit was added to the models (Supplementary table 3). This is most likely due to lack of power because only 45 preterm deliveries had the information about gestational age at last antenatal visit and were included in the gestational age at last antenatal visit-adjusted model.

Comment

The current study indicates that low mHb at late pregnancy is associated with increased risk of preterm delivery and high mHb with increased risk of full-term SGA. These results support the previously published concept of U-shaped association between mHb concentration and the risk of adverse perinatal outcomes (7, 21). However, there are discrepancies between previous publications with respect of this association. One problem related to the generalization of the results from mHb studies

concerns the differences between study populations (22). In low-income countries, the mHb level often relates to the poor nutritional status of the mother contributing to adverse perinatal outcomes. In addition, the prevalence of infectious diseases such as HIV and malaria is higher in the developing countries, which adds further burden to maternal health (5). This socioeconomic and nutritional disparity may lead to severe residual confounding in the analyses. Current study population is located in Finland where standardized antenatal care system and relatively high living standards induce smaller differences in environmental factors affecting the development of the fetus and yet still, abnormal mHb was associated with prematurity and SGA.

Another issue varying between studies relates to the timing of the mHb measurement during pregnancy. Level of mHb changes naturally throughout the pregnancy and it may be critical for the results whether the measurement occurs at early or late pregnancy (20). In the current study, we wanted to evaluate mHb at early and late pregnancy to find out how they contribute to overall risk of adverse perinatal outcomes. Our results indicate that abnormal mHb measured at late pregnancy associates with increased risk of prematurity and SGA. Fetus grows rapidly during the third trimester when iron and other micronutrient demands are specifically high (23). Abnormal mHb may reflect insufficient availability and/or delivery of nutrients to the fetus and specifically at the end of pregnancy alter the rapid growth phase. It is safe to assume that due to systematic antenatal care in Finland, if low mHb was measured at the beginning of the pregnancy, it had been attempted to increase by administration of iron supplements or other medical actions. Interestingly, low mHb at the beginning of pregnancy was in fact associated with decreased risk of SGA in current study. In high-income countries, approximately 60% of the pregnant women with low hemoglobin are estimated to be amenable to iron supplementation (9). Thus, the mothers with low mHb at late pregnancy may be the ones that do not response to iron supplementation and are at increased risk of preterm delivery in the current study. We know that iron supplementation was recommended already in 1960s for pregnant women to prevent gestational anemia (8, 24); however, we do not have information about its administration or iron status of the mother in the current study to research this issue in more detail.

Further variation within mHb studies is added by varying cutoffs for categorical variables of low and high mHb. WHO defines anemia during pregnancy as mHb less than 110 g/l, which is widely used cutoff for low mHb (9). However, discussion about an appropriate cutoff during pregnancy is ongoing as some studies found association only with mHb levels below 100 g/l (25, 26). Furthermore, similar to previous studies located in Finland and Sweden (22, 27), the prevalence of anemia with the 110 g/l cutoff was low in the current study, only approximately 4%. The earlier Finnish study with more stringent cutoff of 100 g/l did not found association between mHb and preterm delivery and SGA, which may result from decreased statistical power due to low number of mothers with “true anemia”

(22). To overcome this issue, we decided to define lowest 10% of the mHb z values as low mHb and highest 10% of the mHb z values as high mHb. These correspond to cutoff values for low mHb of approximately 110 g/l in NFBC1966 and 117 g/l in NFCB1986. For high mHb, cutoff values were 135 g/l and 140 g/l in NFBC1966 and NFBC1986, respectively. Z values were calculated for each cohort and pregnancy time point separately, thus the extremes of mHb are relative for the reference, not for the absolute mHb concentration that may differ throughout the pregnancy.

The mechanism behind the association is unclear. Iron deficiency may contribute to the restricted fetal growth and prematurity through such mechanisms as increased maternal and fetal stress, increased serum norepinephrine production and oxidative damage to erythrocytes and fetoplacental unit (reviewed in (28)). Mothers with low mHb show increased placental vascularization suggesting earlier placental maturity, which may contribute to increased risk of preterm delivery (29, 30). Low mHb may cause chronic hypoxia which in turn may induce a stress response with increased placental corticotropin-releasing hormone (CRH) production. During normal pregnancy, a rapid increase in bioavailable CRH induces labor and if this occurs too early, it may induce preterm delivery (28). High mHb, specifically during late pregnancy may indicate incomplete hemodilution and may lead to fetal hypoxia due to increased blood viscosity and impairment of maternal-fetal exchange and contribute to the risk of SGA (1). Further studies located in high-income countries as well as deeper mechanistic understanding are needed with respect of association between mHb and fetal growth.

Strengths and weaknesses of the study

Large sample size in a homogenous population is major strength of the current study. Universal antenatal care available in Finland and high standard of living offer less variation in the environmental factors affecting the intrauterine development of the child. First limitation is that we do not have reliable information about exact gestational age at mHb measurements from all study subjects in the current study. The measurement timing is specifically important when prematurity is assessed because mHb begins to naturally increase after 30 weeks of gestation. To overcome this, we conducted series of sensitivity analyses that showed similar results as our main models indicating that the association between low mHb at late pregnancy and prematurity is not mediated by the timing of mHb measurement. Other limitations relate to the lack of clinical measures of fetal hypoxia and iron metabolism. Our data suggests that there may be distinct outcomes depending on the mother's responsiveness on iron supplementation. The current study shows that both low and high mHb may indicate increased risk for distress in the developing child. Mechanistic studies are warranted to reveal the possible causal influence of abnormal mHb on perinatal outcomes.

Conflict of Interest

The authors report no conflict of interest.

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Tables

Table 1. Characteristics of mothers and singleton newborns in the pooled sample and stratified by the cohort.

	Pooled	NFBC1966	NFBC1986	p value *
Early maternal hemoglobin				< 0.0005 [A]
Reference, n (%)	14662 (77.4)	7762 (77.8)	6900 (76.8)	
Low, n (%)	1888 (10)	827 (8.3)	1061 (11.8)	
High, n (%)	2403 (12.7)	1384 (13.9)	1019 (11.3)	
Late maternal hemoglobin				< 0.0005 [A]
Reference, n (%)	15848 (79.1)	9118 (81.4)	6730 (76.1)	
Low, n (%)	1978 (9.9)	926 (8.3)	1052 (11.9)	
High, n (%)	2209 (11)	1153 (10.3)	1056 (11.9)	
Maternal age, years (SD)	27.8 (6.2)	27.8 (6.7)	27.8 (5.5)	0.911
Pre-pregnancy BMI, kg/m2 (SD)	22.8 (3.4)	23.1 (3.2)	22.4 (3.5)	< 0.0005
Maternal smoking				< 0.0005 [A]
No, n (%)	15581 (76.9)	8827 (78.1)	6754 (75.4)	
Yes, but stopped, n (%)	986 (4.9)	753 (6.7)	233 (2.6)	
Yes, n (%)	3701 (18.3)	1728 (15.3)	1973 (22)	
Maternal SES				< 0.0005 [B]
Professional, n (%)	3697 (18.4)	1435 (12.6)	2262 (25.9)	
Skilled worker, n (%)	5981 (29.7)	2469 (21.7)	3512 (40.2)	
Unskilled worker, n (%)	3539 (17.6)	985 (8.7)	2554 (29.2)	
Homemaker, n (%)	6906 (34.3)	6497 (57.1)	409 (4.7)	
Parity				0.076
First child, n (%)	6813 (33.2)	3770 (32.7)	3043 (33.9)	
Second or later child, n (%)	13712 (66.8)	7768 (67.3)	5944 (66.1)	
Maternal hypertensive disorders				< 0.0005 [C]
Normotensive, n (%)	13535 (83)	6460 (76.3)	7075 (90.3)	
Gestational hypertension, n (%)	1253 (7.7)	983 (11.6)	270 (3.4)	
Pre-eclampsia, n (%)	423 (2.6)	241 (2.8)	182 (2.3)	
Chronic hypertension, n (%)	881 (5.4)	668 (7.9)	213 (2.7)	
Superimposed pre-eclampsia, n (%)	208 (1.3)	116 (1.4)	92 (1.2)	
Birth weight, grams (SD)	3518 (556)	3478 (560)	3570 (546)	< 0.0005
Gestational age, weeks (SD)	39.9 (1.9)	40.0 (2.1)	39.8 (1.7)	< 0.0005
Boys, n (%)	10529 (51.2)	5917 (51.2)	4612 (51.3)	0.978
Preterm delivery, n (%)	1003 (5.0)	610 (5.5)	393 (4.5)	0.002
Full-term SGA, n (%)	1746 (9.2)	1172 (11.1)	574 (6.9)	< 0.0005
Full-term LGA, n (%)	1773 (9.4)	908 (8.6)	865 (10.3)	< 0.0005

* Comparison between NFBC1966 and NFBC1986

[A] $p < 0.05$ between all mHb categories

[B] $p < 0.05$ between all SES categories except professional vs. skilled worker

[C] $p < 0.05$ between all hypertensive disorder categories except normotensive vs. superimposed pre-eclampsia, gestational hypertension vs. chronic hypertension and pre-eclampsia vs. superimposed pre-eclampsia

Table 2. Association between maternal hemoglobin during pregnancy and preterm delivery. OR, odds ratio; 95% CI, 95% confidence interval; p, p-value according to Wald's test, significant when $p < 0.0125$.

		Base model			Model 1[1]			Model 2[2]		
Outcome	**mHb**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Preterm delivery	**Low early**	1.17	[0.94, 1.44]	0.154	1.23	[0.97, 1.55]	0.088	1.24	[0.97, 1.58]	0.084
	High early	1.10	[0.90, 1.34]	0.344	1.05	[0.84, 1.31]	0.660	1.11	[0.89, 1.40]	0.357
	Low late	**1.56**	**[1.27, 1.91]**	**< 0.0005**	**1.61**	**[1.29, 2.02]**	**< 0.0005**	**1.57**	**[1.24, 1.99]**	**< 0.0005**
	High late	0.78	[0.61, 1.01]	0.055	0.73	[0.55, 0.97]	0.028	0.74	[0.55, 0.99]	0.045

[1] Model 1 adjusted for cohort, maternal smoking and maternal hypertensive disorders

[2] Model 2 adjusted for cohort, maternal smoking, maternal hypertensive disorders, pre-pregnancy BMI, maternal SES, parity and maternal age

Table 3. Association between maternal hemoglobin during pregnancy and full-term small and large for gestational age (SGA and LGA, respectively). OR, odds ratio; 95% CI, 95% confidence interval; p, p-value according to Wald's test, significant when $p < 0.0125$.

		Base model			Model 1[1]			Model 2[2]		
Outcome	**mHb**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
SGA	**Low early**	**0.75**	**[0.62, 0.91]**	**0.004**	**0.75**	**[0.60, 0.94]**	**0.012**	**0.74**	**[0.58, 0.93]**	**0.011**
	High early	1.16	[1.00, 1.35]	0.055	1.07	[0.90, 1.28]	0.446	1.16	[0.96, 1.39]	0.123
	Low late	0.88	[0.74, 1.06]	0.170	0.83	[0.67, 1.03]	0.086	0.85	[0.68, 1.06]	0.147
	High late	**1.25**	**[1.08, 1.45]**	**0.003**	**1.33**	**[1.13, 1.58]**	**0.001**	**1.32**	**[1.10, 1.58]**	**0.002**
LGA	**Low early**	**1.23**	**[1.05, 1.44]**	**0.011**	**1.26**	**[1.06, 1.51]**	**0.011**	1.24	[1.03, 1.50]	0.025
	High early	0.95	[0.81, 1.11]	0.500	0.91	[0.76, 1.09]	0.296	0.82	[0.67, 1.00]	0.049
	Low late	1.23	[1.05, 1.44]	0.011	1.25	[1.05, 1.50]	0.014	1.23	[1.01, 1.49]	0.035
	High late	1.01	[0.87, 1.19]	0.869	0.96	[0.80, 1.15]	0.632	1.03	[0.85, 1.24]	0.792

[1] Model 1 adjusted for cohort, maternal smoking and maternal hypertensive disorders
[2] Model 2 adjusted for cohort, maternal smoking, maternal hypertensive disorders, pre-pregnancy BMI, maternal SES, parity and maternal age

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Supplementary table 1. Multinomial logistic regression for maternal hemoglobin (mHb) and perinatal outcomes in pooled, NFBC1966 and NFBC1986 data. OR, Odds ratio; 95% CI, 95% confidence interval; p, p-value according to Wald's test, significant when p < 0.0125; SGA, small for gestational age; LGA, large for gestational age.

a) Preterm delivery

		Pooled				NFBC1966				NFBC1986			
mHb	Model	OR	95% CI		p	OR	95% CI		p	OR	95% CI		p
			lower	upper			lower	upper			lower	upper	
Low early	Base	1,17	0,94	1,44	0,157	1,02	0,74	1,40	0,922	1,38	1,03	1,83	0,029
	Model 1	1,23	0,97	1,56	0,081	1,02	0,71	1,47	0,902	1,43	1,05	1,94	0,023
	Model 2	1,24	0,97	1,59	0,079	0,98	0,66	1,45	0,916	1,48	1,08	2,02	0,014
High early	Base	1,12	0,90	1,39	0,323	1,15	0,85	1,56	0,375	1,14	0,84	1,57	0,397
	Model 1	1,10	0,86	1,41	0,437	1,08	0,75	1,55	0,665	1,13	0,80	1,59	0,481
	Model 2	1,18	0,91	1,52	0,209	1,15	0,79	1,68	0,457	1,21	0,86	1,72	0,276
Low late	Base	**1,58**	**1,29**	**1,93**	**< 0.0005**	1,33	0,97	1,82	0,078	**1,77**	**1,36**	**2,31**	**< 0.0005**
	Model 1	**1,64**	**1,31**	**2,05**	**< 0.0005**	1,33	0,93	1,91	0,115	**1,85**	**1,39**	**2,47**	**< 0.0005**
	Model 2	**1,60**	**1,26**	**2,02**	**< 0.0005**	1,31	0,89	1,94	0,175	**1,81**	**1,34**	**2,45**	**< 0.0005**
High late	Base	0,87	0,67	1,12	0,275	0,97	0,70	1,34	0,846	0,73	0,48	1,12	0,148
	Model 1	0,81	0,61	1,09	0,166	0,98	0,68	1,41	0,924	0,62	0,38	1,01	0,056
	Model 2	0,83	0,62	1,13	0,236	1,04	0,71	1,52	0,834	0,62	0,37	1,02	0,062

b) Full-term SGA

		Pooled				NFBC1966				NFBC1986			
mHb	Model	OR	95% CI		p	OR	95% CI		p	OR	95% CI		p
			lower	upper			lower	upper			lower	upper	
Low early	Base	**0,74**	**0,61**	**0,90**	**0,003**	0,79	0,61	1,03	0,080	0,77	0,57	1,03	0,078
	Model 1	**0,75**	**0,59**	**0,94**	**0,011**	0,71	0,51	0,98	0,040	0,77	0,56	1,06	0,113
	Model 2	**0,73**	**0,58**	**0,93**	**0,010**	0,67	0,48	0,96	0,027	0,78	0,56	1,07	0,121
High early	Base	1,10	0,93	1,30	0,280	1,14	0,90	1,44	0,284	1,18	0,92	1,52	0,203
	Model 1	1,07	0,87	1,31	0,518	1,12	0,84	1,49	0,432	1,04	0,78	1,39	0,805
	Model 2	1,15	0,93	1,42	0,199	1,26	0,93	1,69	0,133	1,07	0,79	1,45	0,684
Low late	Base	0,88	0,74	1,06	0,173	1,04	0,83	1,30	0,764	0,78	0,58	1,04	0,094
	Model 1	0,82	0,67	1,02	0,073	0,94	0,71	1,23	0,633	0,70	0,50	0,97	0,032
	Model 2	0,84	0,67	1,05	0,129	0,97	0,72	1,30	0,821	0,71	0,50	0,99	0,044
High late	Base	**1,29**	**1,10**	**1,50**	**0,001**	**1,34**	**1,11**	**1,61**	**0,002**	1,16	0,87	1,53	0,306
	Model 1	**1,30**	**1,09**	**1,56**	**0,004**	**1,38**	**1,11**	**1,72**	**0,004**	1,16	0,85	1,58	0,357
	Model 2	**1,29**	**1,07**	**1,56**	**0,009**	**1,42**	**1,13**	**1,80**	**0,003**	1,07	0,77	1,49	0,686

c) Full-term LGA

		Pooled				NFBC1966				NFBC1986			
mHb	Model	OR	95% CI		p	OR	95% CI		p	OR	95% CI		p
			lower	upper			lower	upper			lower	upper	
Low early	Base	**1,23**	**1,05**	**1,44**	**0,010**	1,30	1,02	1,66	0,034	1,14	0,92	1,41	0,220
	Model 1	1,25	1,05	1,50	0,013	1,34	1,01	1,78	0,045	1,20	0,95	1,50	0,120
	Model 2	1,23	1,02	1,49	0,030	1,31	0,96	1,80	0,093	1,19	0,94	1,51	0,147
High early	Base	0,95	0,80	1,14	0,598	1,06	0,82	1,39	0,645	0,85	0,67	1,08	0,174
	Model 1	0,83	0,68	1,03	0,086	0,97	0,71	1,34	0,871	0,74	0,56	0,98	0,034
	Model 2	**0,72**	**0,57**	**0,91**	**0,005**	0,81	0,56	1,16	0,248	**0,67**	**0,50**	**0,90**	**0,008**
Low late	Base	1,22	1,04	1,43	0,014	1,29	1,03	1,63	0,029	1,12	0,90	1,39	0,308
	Model 1	1,25	1,04	1,50	0,015	1,34	1,01	1,77	0,041	1,19	0,94	1,51	0,142
	Model 2	1,22	1,01	1,48	0,039	1,26	0,93	1,71	0,140	1,21	0,95	1,55	0,130
High late	Base	0,96	0,81	1,13	0,605	1,01	0,80	1,26	0,947	0,91	0,70	1,17	0,449
	Model 1	0,93	0,76	1,12	0,436	1,00	0,76	1,30	0,977	0,86	0,65	1,14	0,290
	Model 2	0,99	0,81	1,21	0,915	1,09	0,82	1,45	0,556	0,90	0,67	1,21	0,486

Models

Base: mHb

Model 1: mHb + cohort (for pooled data) + maternal smoking + maternal hypertensive disorders

Model 2: mHb + cohort (for pooled data) + maternal smoking + maternal hypertensive disorders + pre-pregnancy BMI+ socioeconomic status + parity + maternal age at delivery