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Differences in body mass index between siblings who are discordant for exposure to antenatal maternal smoking

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Running head. Maternal smoking in pregnancy – a sibling analysis

ABSTRACT

Background. Maternal smoking during pregnancy is associated with increased childhood body mass index (BMI) but the relationship may be due to confounding by maternal factors. This study tested the hypothesis that siblings born to mothers who begin to smoke between pregnancies will have higher BMI than older unexposed siblings.

Methods. Maternal details from the Aberdeen Maternity and Neonatal Databank were linked to the Study of Trends in Obesity in North East Scotland which holds offspring BMI at five years of age. Change in maternal smoking status between pregnancies was linked to offspring BMI and also to the difference in BMI between siblings.

Results. Maternal smoking status in successive pregnancies was linked to child BMI at age 5 years in 6,581 mother-child pairs of whom 718 included sibling pairs. Children whose mothers had quit, started smoking or smoked in consecutive pregnancies had higher BMI compared to those not exposed to maternal smoking. Siblings born after onset of maternal smoking had higher mean BMI z score or (0.20 95% confidence interval CI ~~(0.03, 0.38)~~) compared to unexposed older siblings.

Mean BMI z score was also higher by mean of 0.10 ~~(95% CI 0.00, 0.19)~~ in younger sibling compared to older siblings born to mothers who smoked in both pregnancies. BMI z score was not significantly different between siblings whose mothers quit between pregnancies.

Conclusions. In utero exposure to maternal smoking during pregnancy may increase the likelihood of increased BMI in childhood.

Key words. Child, Obesity, Pregnancy, Smoking

INTRODUCTION

The prevalence of childhood obesity and overweight has risen over the last 20 years to 30% in the UK and 50% in the US,¹ with this rise being called the epidemic of our lifetime.² Childhood obesity is a complex condition where genetic factors and environmental exposures during antenatal and postnatal life may contribute towards an “obesogenic environment”.^{1,3} Maternal smoking during pregnancy has been identified as a potential risk factor for childhood overweight or obesity in at least five systematic reviews,⁴⁻⁸ and these observations suggest that maternal smoking increases the odds of child obesity and overweight by between 20 and 50%.

In this study we linked maternal smoking status during pregnancy to offspring BMI at five years of age. Within this large dataset we identified siblings discordant for maternal smoking in pregnancy and tested the hypothesis that siblings born after onset of maternal smoking will have higher BMI compared to older unexposed siblings.

METHODS

Study design

This was a linkage study where self-reported smoking status (smoking or not) in pregnant women was linked to their offspring’s obesity status and body mass index (BMI) at age five years. Details were obtained from the Aberdeen Maternity and Neonatal Databank (AMND)⁹ and the Study of Trends in Obesity in North East Scotland dataset (STONES)¹⁰; the AMND and STONES are both based on the population of North East Scotland and hold routinely collected data in mothers and children respectively. The community health index number (CHI), a unique patient identifier used widely in Scotland since 1997, was used for linkage for children born between 1997 and 2005 and BMI measured between 2002 and 2010. The study was approved by the North of Scotland Research

Ethics Service, the AMND steering committee and the Caldicott guardian for National Health Service Grampian.

Maternal details from Aberdeen Maternity and Neonatal Databank

Maternal smoking status between successive pregnancies was categorised as: Never smoked (i.e. did not smoke in either pregnancy), quit (i.e. smoked in the first but not the second pregnancy), started smoking (i.e. smoked during the second but not the first pregnancy) and always smoked (i.e. smoked in both pregnancies). Separate quit and started smoking categories were included for two reasons: first, to accommodate anticipated differences in the characteristics (including lifestyle factors) for mothers who quit or started smoking between pregnancies are likely to differ; second, and also to recognise the differences in exposure of the ovum from which the older sibling originated: for mothers who quit between pregnancies both the -the ova which became- older and younger siblings were exposed (the latter as an ova) whereas for mothers who started smoking between pregnancies, only the younger sibling was exposed ~~born before onset of maternal smoking were not exposed to products of tobacco smoke whereas ova which became older siblings born before smoking cessation were exposed.~~ The number of cigarettes smoked was not available in our dataset. Socioeconomic status was defined by the Carstairs index, which comprises four indicators (lack of car ownership, low occupational social class, overcrowded households and male unemployment). Mothers who were more than 16 weeks pregnant at their first antenatal visit were excluded because beyond this gestation maternal weight is not an accurate reflection of pre-pregnancy weight as it also includes the weight of the growing pregnancy. Twin and other multiple pregnancies were excluded. Change in maternal weight between pregnancies was categorised: $\pm 3\%$ was the reference ¹¹; $\pm 3-4.99\%$; $\pm 5-9.99\%$; and $\pm \geq 10\%$ (5% and 10% changes are “realistic targets” for weight loss considered to bring health benefits¹²). Gestational weight gain was not available in our linked dataset.

STONES

The STONES database holds routinely collected height and weight measurements of children assessed between 1970 and 2010 at school entry at an average age of 5.5 years¹⁰. The International Obesity Task Force (IOTF) criteria for childhood weight categories were used to define obese, overweight, thinness and healthy weight¹³ and Z scores for BMI were derived using the UK 1990 standard¹⁴.

Statistical analysis

For every mother-child pair the child weight category (thin, healthy weight, overweight, obese) was related to maternal smoking status (yes/no) a fixed effect, using multinomial multilevel logistic modelling adjusting for factors (i.e. child sex, maternal weight category, socioeconomic status, parity, maternal age and birth weight z score), all fixed effects. A two level multivariate model (child level 1, mother level 2) was used to relate the BMI z score of children and changing maternal smoking status between pregnancies adjusting for factors, again all as fixed factor effects. The second analysis was repeated but with difference in BMI z score (younger sibling minus older sibling) as the outcome variable. ~~All analyses were conducted in either SPSS (version 22.0.0.1) or Stata version 13 and a p value of <0.05 was assumed to be significant unless otherwise specified~~

RESULTS

Study population

There were 59,975 children in the STONES database where a CHI number was recorded and maternal and child records were ultimately linked in 26,961 pairs (44%). Reasons for data not being linked are described in the on line supplement. The children for whom BMI was linked to maternal smoking status were representative of the whole STONES population for age, sex and BMI centile, table 1. Within the 26,961 matched mother-child pairs, there were 5,863 mothers with >1 linked

pregnancies. The prevalence of maternal smoking was 25.8% in 1997 and 20.0% in 2005 (see table 2 in the supplementary material). The mean interval between deliveries was 3.1 (SD 2.3) years, the mean change in maternal weight between pregnancies was +2.3 kg (SD 6.1).

Maternal smoking and child weight categories

Maternal smoking in pregnancy was associated with an increased odds ratio (OR) with 95% Confidence Interval (CI) for childhood obesity (OR 1.8 (95% CI 1.6, 2.1)) and overweight (OR 1.5 95% CI (1.3, 1.6)) and reduced OR for offspring being thin (OR 0.7 (95% CI 0.6, 0.8)) relative to not smoking in pregnancy (see table 3 in the supplementary material).

Change in maternal smoking between pregnancies and offspring outcomes (without sibling comparison)

Childhood obesity. The OR for obesity was increased for children whose mothers started smoking between pregnancy (OR 2.0 (95% CI 1.1, 3.6)) or who smoked in both pregnancies (OR 1.8 (95% CI 1.3, 2.6)) compared to never smoked, independent of maternal weight, weight gain, socioeconomic status and the child's sex and birth weight, table 2. Children whose mothers quit were not at increased risk for obesity compared to those whose mothers never smoked (OR 1.6 (95% CI 1.0, 2.5)), table 2.

Childhood BMI z score. The mean BMI z score was increased among those children whose mothers always smoked (0.32 z score (95% CI 0.24, 0.40)), quit smoking between pregnancies (0.29 z score (95% CI 0.18, 0.40)) and who started smoking between pregnancies (0.22 z score (95% CI 0.07, 0.36)) compared to children whose mothers never smoked, table 3. In this analysis higher child BMI was associated with maternal weight gain between pregnancies of $\geq 10\%$, maternal obesity, deprivation and younger maternal age at delivery, table 3.

Change in maternal smoking between pregnancies and offspring outcomes (with sibling

comparison) In the sibling analysis, BMI z score was higher for younger compared to older siblings when their mother either started smoking between pregnancies (mean difference 0.19 [95% CI 0.01, 0.36]) or smoked during both pregnancies (0.10 [95% CI 0.01, 0.20]), table 3. Younger siblings also had higher BMI z score in association with deprivation but not with maternal weight status or weight gain between pregnancies, table 3.

COMMENT

This study used linkage of routinely collected data to test the hypothesis that children born after onset of maternal smoking will have higher BMI compared to older unexposed siblings. The initial analysis of more than 25,000 mother-child pairs confirmed previous reports⁴⁻⁸ of an association between maternal smoking during pregnancy and an increase in odds ratio of 1.37-1.50⁴⁻⁷ for overweight and of 1.52 for obesity⁸ in the child. Next we report that compared to peers whose mothers had never smoked whilst pregnant, children whose mothers had smoked in either or both pregnancies had increased odds for obesity and overweight (table 2) and also had higher BMI (table 3). In the sibling analysis, where genetic and family lifestyle factors are less heterogeneous compared to peer comparison, only children whose mothers smoked whilst pregnant had increased BMI when compared to unexposed siblings (table 3). Our hypothesis might be extended to predict that cessation between pregnancies would be associated with reduced BMI in the younger and unexposed sibling but this was not the case. These findings support the possibility that maternal smoking increases the likelihood of childhood obesity.

A weakness of our study was that smoking status was by self-report and only determined at a single point during pregnancy, and this means that there is undoubtedly some exposure misclassification due to under-reporting of maternal smoking¹⁵. This misclassification could explain why there was apparently no reduction in BMI in the younger child after cessation since their mother may not have

truly quit and/or may have relapsed in the pregnancy later meaning that they were exposed, biasing the findings toward the null. Importantly, misclassification will not explain the association between increased BMI and new onset and persistent maternal smoking.

Sibling comparison brings a number of strengths and also has some limitations. A strength of the sibling analysis is that genetic and lifestyle factors are less likely to confound associations between disease outcomes and changes in the environment, for example obesity and onset of maternal smoking. A second strength of sibling analysis is that the effect of both maternal and paternal genes on childhood BMI are considered, although in some cases the mother's partner will have changed between pregnancies. The sib-pair design is also useful for accounting those confounders that are time invariant, but not for those which are time variant (for example infant feeding). One limitation of the sibling analysis is that there will be some genetic heterogeneity between the sibling pairs but it is unlikely that genetic variation is consistently different between older and young siblings across the whole population. A second limitation is that the results may not be generalisable to families who have one child

In summary, our study gives novel insight into the complex relationship between maternal smoking and offspring BMI.

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Table 1. Comparison of Details for the Group where Mother's and Child's Weight were Linked Compared to the Whole Population. *500 cases were not included in the final analyses due to ≥ 1 item of missing data.

	Whole population n \leq 59,919	Mother and child weight linked n \leq 29,455	Maternal weight gain linked to child BMI* n=26,961
Child male sex	51.4% (30,799/59,919)	51% (15,135/29,453)	51% (13,830/26,961)
Child mean age (SD), years	5.6 (0.6)	5.6 (0.6)	5.6 (0.6)
Child mean BMI z score (SD)	0.25 (1.11)	0.25 (1.12)	0.24 (1.11)
Proportion of obese children	4.7% (2,625/55,454)	4.8% (1418/29,484)	4.7% (1,270/26,961)
Mean birth weight (SD), g	3412 (567)	3416 (565)	3416 (564)
Mean maternal age at delivery (SD), years	28.9 (5.5)	28.9 (5.5)	28.9 (5.5)
Mean maternal weight (kg)	67.1 (14.0)	67.1 (14.0)	67.2 (14.0)
Mean maternal BMI (SD)	25.2 (5.0)	25.2 (5.0)	25.3 (5.0)
Proportion of obese mothers (i.e. BMI>30kg/m ²)	15.3% (5,211/34,136)	14.9% (4,345/29,119)	15.0% (4,029/26,961)
Proportion of mothers who smoked	23.2% (8311/35,895)	22.2% (6546/29,454)	21.9% (5,912/26,961)
Socioeconomic status (Carstairs)			
1 (Least deprived)		20% (5,841/29,319)	21% (5,460/26,961)
2		33% (9,653/29,319)	33% (8,511/26,961)
3		17% (5,117/29,319)	17% (4,645/26,961)
4		16% (4,628/29,319)	15% (4,123/26,961)
5		6% (1,743/29,319)	6% (1,622/26,961)
6 (Most deprived)		8% (2,337/29,319)	8% (2,160/26,961)
Parity			
1 st live child		47% (14,442/30,616)	47% (12,778/26,961)
1 other sib		36% (11,063/30,616)	36% (11,063/26,961)
2 other sibs		12% (3,658/30,616)	12% (3,168/26,961)
≥ 3 other sibs		5% (1,453/30,616)	5% (1,257/26,961)
Maternal smoking			
Never smoked		76% (5,597/7,410)	76% (5,010/6,611)
Quit		6% (373/7,410)	6% (373/6,611)
Started smoking		3% (250/7,410)	3% (217/6,611)
Always smoked		16% (1,152/7,410)	15% (1,011/6,611)
Percentage Maternal weight change			
$\geq -10\%$		3% (221/7,153)	3% (209/6,518)
-5.0 to -9.9%		8% (509/7,153)	8% (509/6,518)
-3.0 to -4.9%		6% (405/7,153)	6% (405/6,518)
$\pm 3.0\%$		33% (2,160/7,153)	33% (2,160/6,518)
$\pm 3.0\%$		11% (704/7,153)	11% (704/6,518)
+3.0 to +4.9%		20% (1,287/7,153)	20% (1,287/6,518)
+5.0 to +9.9%		19% (1,354/7,153)	20% (1,244/6,518)
$\geq +10\%$			

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Table 2. Risk of a Child being Obese at Five Years or Age Compared to Healthy Weight using a Multinomial, Multilevel Model to Incorporate the Sibling and Mother Relationships. Maternal obesity was defined as body mass index (BMI)>30kg/m², overweight as BMI 25-29 kg/m² and underweight as BMI<18kg/m².

	Child normal n=4960	Odds ratio for child obese n=270 (95% CI)	Odds ratio for child Overweight n=830 (95% CI)	Odds ratio for thinness n=504 (95% CI)
Maternal smoking status				
Never smoked (ref)		1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Quit		1.6 (1.0, 2.5)	1.5 (1.1, 2.0)	0.6 (0.4, 1.0)
Started smoking		2.0 (1.1, 3.6)	1.5 (1.0, 2.2)	1.0 (0.6, 1.7)
Always smoked		1.8 (1.3, 2.6)	1.5 (1.2, 1.8)	0.6 (0.5, 0.8)
Maternal Weight category †				
Underweight		0.2 (0.00, 1.3)	0.5 (0.3, 1.0)	1.6 (1.0, 2.4)
healthy weight (ref)		1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Overweight		2.4 (1.8, 3.1)	1.6 (1.4, 1.9)	0.7 (0.6, 0.9)
obese		3.3 (.4, 4.6)	2.0 (1.6, 2.5)	0.4 (0.3, 0.6)
Percentage Maternal weight change				
≥-10%		1.9 (1.4, 2.7)	1.3 (1.0, 1.6)	1.2 (0.9, 1.6)
-5.0 to -9.9%		1.2 (0.8, 1.7)	1.0 (0.8, 1.3)	0.9 (0.7, 1.2)
-3.0 to -4.9%		1.1 (0.7, 1.8)	0.9 (0.6, 1.1)	1.1 (0.8, 1.5)
±3.0% (ref)		1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
+3.0 to +4.9%		1.3 (0.8, 2.3)	1.0 (0.7, 1.4)	0.9 (0.6, 1.3)
+5.0 to +9.9%		1.3 (0.8, 2.2)	1.0 (0.7, 1.3)	1.0 (0.7, 1.5)
≥+10%		1.4 (0.7, 2.5)	1.1 (0.7, 1.6)	1.4 (0.8, 2.5)
Maternal socioeconomic status (Carstairs)†				
1 (Least deprived)		1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
2		1.2 (0.9, 1.7)	1.1 (1.0, 1.5)	0.8 (0.7, 1.1)
3		1.6 (1.1, 2.4)	1.3 (1.0, 1.6)	0.8 (0.6, 1.1)
4		1.1 (0.7, 1.7)	1.4 (1.1, 1.9)	1.0 (0.7, 1.4)
5		1.7 (0.9, 3.0)	1.1 (0.8, 1.7)	0.8 (0.5, 1.4)
6		1.7 (1.0, 2.8)	1.7 (1.2, 2.2)	0.7 (0.5, 1.1)
Mean maternal age at delivery (SD), years †		1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Male sex		0.6 (0.5, 0.8)	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)
Parity				
1 older sibling (ref)		1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
2 older siblings		0.8 (0.6, 1.1)	1.0 (0.8, 1.2)	1.1 (0.9, 1.4)
≥3 older siblings		0.8 (0.5, 1.2)	0.9 (0.7, 1.1)	1.2 (0.8, 1.7)
Child birth weight (z-score)		1.2 (1.0, 1.4)	1.4 (1.3, 1.5)	0.6 (0.5, 0.7)
Constant		0.0 (0.0, 0.1)	0.1 (0.1, 0.3)	0.2 (0.1, 0.4)

† At first booking unless otherwise stated; ref: reference group

CI: Confidence Interval

Table 3. Child Age-Adjusted BMI (as a z-score) with Respect to Change in Maternal Smoking. Results are presented from a multilevel linear model.

		Without sibling analysis Beta (regression coefficient) for child BMI z score 6580 children and 5862 mothers.	With sibling analysis Beta (regression coefficient) for difference in BMI z score in siblings at five years of age 6318 children and 5639 mothers
	constant	-0.11 (-0.32, 0.10)	-0.20 (-0.42, 0.09)
Maternal smoking status	Never smoked	0.000.00 (Reference)	0.000.00 (Reference)
	Quit	0.29 (0.18, 0.40)	0.05 (-0.09, 0.18)
	Started smoking	0.22 (0.07, 0.36)	0.19 (0.01, 0.36)
	Always smoked	0.32 (0.24, 0.40)	0.10 (0.01, 0.20)
Maternal Weight category †	underweight	-0.37 (-0.53, -0.22)	0.156 (-0.036, 0.348)
	Healthy weight	0.000.00 (Reference)	0.000.00 (Reference)
	overweight	0.31 (0.25, 0.37)	0.059 (-0.014, 0.133)
	obese	0.48 (0.39, 0.56)	-0.052 (-0.152, 0.048)
Maternal weight change	10% or greater gain	0.13 (0.05, 0.20)	0.02 (-0.07, 0.12)
	5-9.9% gain	0.00 (-0.07, 0.07)	0.03 (-0.06, 0.12)
	3-4.9% gain	-0.02 (-0.11, 0.07)	-0.03 (-0.14, 0.08)
	±3.0% (ref)	0.000.00 (Reference)	0.000.00 (Reference)
	-3 to -4.9%	0.03 (-0.08, 0.14)	0.11 (-0.02, 0.25)
	-5 to -9.9%	0.03 (-0.08, 0.13)	0.06 (-0.07, 0.18)
	-10% or greater loss	-0.02 (-0.16, 0.13)	0.06 (-0.12, 0.24)
Maternal socioeconomic status (Carstairs)†	1 (Least deprived)	0.000.00 (Reference)	0.000.00 (Reference)
	2	0.13 (0.06, 0.19)	0.04 (-0.04, 0.13)
	3	0.19 (0.11, 0.27)	0.17 (0.07, 0.27)
	4	0.12 (0.02, 0.21)	0.10 (-0.02, 0.21)
	5	0.13 (-0.01, 0.27)	0.05 (-0.12, 0.22)
	6	0.25 (0.14, 0.36)	0.21 (0.07, 0.34)
	Mean maternal age at delivery (SD), years †	0.00 (-0.01, 0.01)	0.00 (-0.01, 0.01)
	Child sex (Male)	-0.02 (-0.07, 0.04)	-0.02 (-0.08, 0.04)
Parity	1 other sib	0.000.00 (Reference)	0.000.00 (Reference)
	2 other sibs	-0.06 (-0.12, -0.00)	-0.00 (-0.08, 0.07)
	3 or more other sibs	-0.09 (-0.19, 0.00)	0.02 (-0.10, 0.13)
	Child birth weight (z-score)	0.21 (0.18, 0.24)	0.10 (0.07, 0.14)
	Log likelihood:	-9603.56	-10350.29
	BIC:	19470.89	20963.13
	AIC:	19267.13	20760.60
	ICC:	null model = 0.32 – reduces to 0.26	null model = 0.000 – reduces to 0.000

† At first booking unless otherwise stated

For Review Only

Online supplement

For Review Only

Reasons for children in STONES cohort not being linked to maternal smoking status

17% of the STONES population were born in a region of North East Scotland with a maternity unit which is separate from the Aberdeen maternity Hospital. 3% of births occurred at home or in small rural maternity units. In 3890 pregnancies, the mother was >16 weeks pregnant when weighed and in 1216 mother-child pairs there were missing measurements for child and/or mother. Children attending schools in Moray were slightly younger than the whole STONES population (5.4 versus 5.6 years) and had a lower prevalence of obesity (3.4% versus 4.0%), see table 1 below.

Table 1. Comparison of details of STONES participants attending schools in Moray and not included in the present analysis with all participants. *p<0.05 compared to whole population

	Whole STONES population	Children attending schools in Moray
Child male sex	52% (104223/202118)	52% (18015/34647)
Child mean age (SD), years	5.6 (0.2) n=190317	5.4 (0.4) n=32163*
Child mean BMI z score (SD)	0.20 (1.09) n=188626	0.10 (1.19) n=31913*
Proportion of obese children	4.0% (7389/188897)	3.4% (1080/31994)*

Table 2. Proportion and number of pregnant mothers who were self-reported smokers in the years 1997 to 2006, i.e. when maternal and child records were linked.

	Proportion of smokers	Number of smokers	Number of non-smokers
1997	25.8%	557	1606
1998	23.0%	503	1685
1999	23.7%	459	1475
2000	21.8%	448	1608
2001	20.8%	413	1573
2002	23.2%	473	1565
2003	23.6%	529	1713
2004	19.9%	524	2108
2005	20.0%	523	2095

Table 3: Risk of Childhood Obesity, Overweight and Thinness at Age Five Years Relative to Maternal Smoking during Pregnancy. The reference category was children who were not obese, overweight or thin. The results are from a multinomial, multilevel model to incorporate the sibling and mother relationships. Data from 26,961 children and 20,594 mothers were included.

			Obese Child	Overweight Child	Thin Child
		n	OR (95%CI) p value	OR (95%CI) p value	OR (95%CI) p value
Maternal smoking		5808	1.84 (1.60, 2.12) *	1.45 (1.32, 1.59) *	0.70 (0.62, 0.80) *
Maternal Weight category ‡	Obese	3958	4.84 (4.18, 5.61) *	2.22 (2.01, 2.45) *	0.64 (0.55, 0.76) *
	Overweight	7172	2.30 (1.99, 2.66) *	1.56 (1.43, 1.70) *	0.74 (0.66, 0.83) *
	healthy(ref)	14639	1	1	1
	Thin	675	0.32 (0.14, 0.71) †	0.62 (0.45, 0.86) †	1.85 (1.50, 2.28) *
Maternal socio-economic status ‡	Least deprived(ref)	5418	1	1	1
	2	8824	1.20 (1.00, 1.44)	1.17 (1.05, 1.30) †	0.91 (0.80, 1.04)
	3	4479	1.36 (1.11, 1.66) †	1.10 (0.97, 1.25)	0.90 (0.77, 1.05)
	4	3963	1.34 (1.08, 1.66) †	1.32 (1.16, 1.50) *	1.02 (0.87, 1.19)
	5	1595	1.54 (1.18, 2.01) †	1.19 (0.99, 1.42)	1.17 (0.95, 1.43)
	6	2165	1.69 (1.32, 2.15) *	1.41 (1.20, 1.65) *	0.97 (0.79, 1.18)
Parity	1 st live child (ref)	12527	1	1	1
	1 other sib	9571	0.78 (0.68, 0.89) *	0.82 (0.75, 0.90) *	1.15 (1.04, 1.28) †
	2 other sibs	3111	0.72 (0.59, 0.88) *	0.83 (0.73, 0.94) †	1.15 (0.98, 1.35)
	≥3 other sibs	1235	0.68 (0.51, 0.90) †	0.80 (0.66, 0.96)	1.35 (1.07, 1.69)
Year of booking, 1992 (ref)		26444	n/s ^a	n/s	n/s
Maternal age at delivery (y)		26444	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Sex (Boy)		13586	0.62 (0.55, 0.70) *	0.69 (0.64, 0.74) *	1.11 (1.01, 1.21)
Birth weight (z)		26444	1.30 (1.22, 1.39) *	1.30 (1.25, 1.35) *	0.66 (0.63, 0.69) *
Constant		26444	0.06 (0.03, 0.11) *	0.21 (0.15, 0.31) *	0.08 (0.05, 0.13) *
Model Diagnostics		Log Likelihood= -20975.817; BIC =42868.085; AIC = 42131.634			

*p<0.002; † p<0.01; ‡At first booking unless otherwise stated

n/s: not significant at p<0.05 [except ^a Year 2006: OR (95%CI) 0.55 (0.32, 0.92), p= 0.023, n= 52]; ref: reference group